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U.S. FOOD AND DRUG ADMINISTRATION
Office of Orphan Products Development

TISSUE AGNOSTIC THERAPIES IN ONCOLOGY:
REGULATORY CONSIDERATIONS FOR ORPHAN DRUG DESIGNATION
PUBLIC WORKSHOP

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P R O C E E D I N G S

OPENING REMARKS

DR. LEWIS: Good morning, everybody.

We thank you for joining us today at the Great Room at White Oak Campus of

FDA. We also have many who are attending on webcast online and we welcome you as well.

I'm Debra Lewis. I'm the Acting Director of Orphan Products Development and I thank you for joining us today at our regulatory considerations for orphan drug designation and tissue agnostic therapies in oncology.

This is our public workshop. We are glad to have you with us and we're very excited on this excellent day that Commissioner Scott Gottlieb will be doing our welcoming remarks. Dr. Gottlieb is just one day shy of one year as our 23rd FDA Commissioner and I think most folks recognize he's taken a huge commitment to the rare disease community in developing rare disease products.

In orphan products, you may have seen we now have a commitment to 90 day response for our orphan drug designations. We're able to sustain this through

1 our modernization plan. And not only has Dr. Gottlieb
2 supported us in this endeavor, but also was very
3 instrumental in bringing about this meeting today.

4 So it's with great pleasure that I introduce
5 to you Dr. Scott Gottlieb, Commissioner of the Food and
6 Drug Administration.

7 (Applause)

8 WELCOME

9 DR. GOTTLIEB: Thanks a lot. Thanks for
10 having me here today. I actually didn't
11 realize it's been a year. It feels like it's a little
12 longer than that.

13 I want to thank you for the opportunity to be
14 here and really commend the group on the remarkable
15 work that's been done over the last year with respect
16 to the orphan drug program. It really owes to the
17 dedication of the professional staff in that office and
18 across the whole Agency. And that dedication to these
19 issues that we've made, I think, some meaningful
20 progress in advancing the policy related to these
21 issues and some of the adjacent issues.

22 We're seeing right now tremendous promise and

1 opportunity for the ability to understand target
2 diseases and the underlying molecular basis of disease
3 much differently than we did in the past. It's much
4 less common today when a new medicine's put into
5 development where the biological basis and rationale
6 for how drugs should work isn't clearly understood at
7 the very outset.

8 In fact, I'd say more and more if you look at
9 what's going on the investment side of healthcare and
10 the life science sector, having a firm understanding of
11 the mechanism of action is increasingly a prerequisite
12 to funding a new drug development program.

13 And I can tell you that with some firsthand
14 experience having worked on the venture capital side of
15 this industry before coming into FDA, that if you
16 didn't have a really clear understanding of the
17 molecular basis for how a drug might work to target a
18 certain disease, it was very hard to get, to get those
19 endeavors funded.

20 In fact, it's just, it's a matter of fact, I
21 think, that a new drug is much less likely to be
22 developed in the first place because of that, if the

1 biological rationale for the molecular entity isn't
2 established early in the beginning of the drug
3 development program.

4 This wasn't always the case and it wasn't the
5 case just a short time ago. If you look back a few
6 decades ago, drug makers were investing in huge
7 facilities to do high throughput screening as they
8 shifted through random hits to find drugs sort of like
9 a needle in a haystack. Now medicine is designed more
10 intelligently against predetermined targets on
11 molecular scaffolds often one atom at a time if you
12 look at what's happening with respect to structure
13 based drug design and technologies like that.

14 This opportunity also compels FDA to adapt our
15 policies to accommodate and leverage these same
16 scientific advances. And so we're here today to talk
17 about some of these openings.

18 Being able to confront disease based on how it
19 develops and not simply how it appears at the time of
20 diagnosis is a key evolution in how we approach
21 scientific research and medicine. And these approaches
22 aren't just theoretical anymore. FDA is opening a door

1 to these methods and embracing new regulatory
2 constructs like basket trials and master protocols that
3 make these approaches easier and more efficient.

4 One of the opportunities we're going to
5 discuss today, which I'm especially focused on, is the
6 prospect of granting orphan designation based on
7 molecular subtype. I want to make sure we're taking
8 every possible step to advance these opportunities. We
9 want to be proactive here. We want to lean forward in
10 these kind of chances.

11 I want to make sure we've properly aligned
12 policy incentives to encourage more intelligent and
13 effective drug development. This challenges us to take
14 up some novel policy questions and that's what we're
15 here today to probe.

16 We're now able to target very rare subtypes of
17 disease with treatments that are tailored in a way that
18 allows them to intervene at the molecular formation of
19 a condition and deliver potentially superior results.
20 In this way we'll have more opportunity to arrest or
21 even prevent disease altogether and not just treat
22 symptoms or manage the slow progression of a condition

1 or the rate of decline in function that comes with
2 certain diseases.

3 This is already happening in multiple clinical
4 settings, but these approaches are most obvious in
5 oncology. Historically FDA has used a histology-based
6 approach to oncology drugs, both in the designation of
7 diseases as orphaned conditions and the approval of
8 indications for treatment of tumor types where it was
9 based on the anatomic site or the histology.

10 Evolving knowledge, though, of the molecular
11 and genetic basis of cancer has led to refinements of
12 the categorization of malignancies based on molecular
13 subtypes. And so the new guidance that we'll develop
14 on tissue agnostic drug development approaches will
15 speak to these opportunities and how we'll grant orphan
16 designation in these situations.

17 We've already granted three such orphan
18 designations, two in cancer and one for a rare
19 inherited eye condition called retinal dystrophy.
20 These same approaches in principles may also lead to
21 much more efficient development programs. In cases
22 where we can generalize a response based on a molecular

1 subtype, successful basket trials based on biomarker
2 type will be more efficient, faster, and cheaper,
3 allowing patients to access scientific advances
4 potentially much sooner.

5 And so, among the questions we'll be taking up
6 today, the evidence needed to consider a biomarker as
7 defining a tissue agnostic disease for purposes of
8 orphan designation. We'll also ask questions about how
9 FDA should approach requests for a product intended to
10 treat, for the treatment of, a tissue agnostic disease as well as
11 histology-specific disease.

12 In very short order, it seems clear that our
13 understanding of diseases is changing from a site and
14 tissue orientation to a molecular basis, and this is
15 especially true, as I said, in oncology. With this
16 medical paradigm, our approach to medicine will be
17 transformed through more tailored therapies aimed at
18 molecular targets.

19 Today we're going to be advancing the
20 discussion on how we can capitalize on these scientific
21 opportunities as a matter of policy and how FDA can
22 adapt its approaches to embrace and foster the

1 development of these new scientific approaches.

2 I want to thank you all for joining us. I
3 especially want to thank the professional staff of FDA
4 that have been working very hard on making these kinds
5 of opportunities available for patients. Thanks a lot.

6 (Applause)

7 MEETING OVERVIEW AND GOALS

8 DR. LEWIS: Thank you. Commissioner Gottlieb, we
9 really appreciate our welcome, getting us off onto a
10 good course. I have a few just administrative
11 announcements I want to make sure folks know. Silence
12 your telephones. If you have not signed in at the
13 registration desk outside, please do so. They can talk
14 to you about lunch plans, as well as get you set for
15 that.

16 For our online attendees, there's an e-mail.
17 If you have issues or problems you can e-mail into the
18 OOPDorphanevents@fda.hhs.gov. And I thank our crew of
19 logistics experts over here for keeping us straight
20 through the day.

21 I also want to note as Dr. Gottlieb said, that
22 the Office of Orphan Products has been just tremendous

1 in support of all of our programs in doing this. I
2 have some acknowledgments up on the screen. We had a
3 meeting workgroup which Christine Mueller
4 and Dev Jillapalli, Medical Officers from
5 Orphan Products, have done an outstanding job of trying
6 to corral us and bring us together on these issues.

7 I also want to thank the rest of the meeting
8 workgroup which is up on the screen, partially from
9 Orphan Products Development, partially from the, our
10 oncology colleagues in CDER. From as well OMPT who's
11 provided us tremendous logistics for today.

12 The whole group has been great across FDA,
13 including we appreciate even going to have some backup
14 today if we need on testing issues. We have that from
15 CDRH. They'll be joining us as we get into the panel
16 discussions and be available.

17 I want to talk a little bit about our
18 panelists. They've been coming from many areas. We've
19 asked different groups and we thank them to give us
20 suggestions on how to get good representation for many
21 areas, whether it is from the, the development side,
22 the research side, patient representation, the getting

1 access to products, how do all these things come
2 together, as well as just the expertise in the
3 scientific area. So, I will show you a list right now
4 of our panelists, but we'll meet them more closely a
5 little bit later in our program.

6 As you can see from the agenda, we'll start
7 with some presentations. So, I'm not going to go
8 through all of my panelists right now. Instead I'm
9 going to go, to talk a little bit about our agenda.

10 First today we'll have a little bit of time
11 where we meet the issues. We'll talk about the
12 science, we'll talk about the perspectives from
13 oncology, and we'll have a little bit of a background,
14 kind of a 101 on designation exclusivity so that when
15 we get to the panel discussion we're really prepared to
16 go.

17 So it's, I want to get started if we can with
18 our first presentation and that will be provided by one
19 of our panelists, Dr. David Hong. Dr. Hong is from
20 University of Texas MD Anderson Cancer Center, the
21 Deputy Chair Department of Investigational Cancer
22 Therapeutics, Division of Cancer Medicine, and he's

1 going to get us set with some background on the
2 scientific questions and clinical considerations. So
3 thank you very much, Dr. Hong.

4 PRESENTATION - SCIENTIFIC BACKGROUND OF TISSUE AGNOSTIC
5 DRUG DEVELOPMENT

6 DR. HONG: Thank you. I want to thank Deb and
7 Dr. Gottlieb and the organizers of this workshop for
8 inviting me here to talk.

9 So I'll tell you, it is an incredibly exciting
10 time in oncology, and as an oncologist and as a
11 clinical trialist, you know, I never anticipated that
12 we would actually even get to this time of kind of
13 tumor agnostic therapy. And since the recent approval
14 of pembrolizumab, it's really kind of opened up a lot
15 of interesting questions and perspectives. Okay.

16 DR. LEWIS: I'm back. I would like to -- oh,
17 I'm only going to, in for a moment and mention the
18 importance of this meeting for us. As we talk about,
19 just as Dr. Hong was saying, the, the policy questions
20 that have come up for us in Orphan Products have raised
21 a lot of great, how the science and the policy come
22 together. And it's such an exciting time that we've

1 had to start grappling with these and I think we are
2 ready for a fantastic look from Dr. Hong about these
3 issues.

4 DR. HONG: And, great. So, these are my
5 disclosures. So, you know, this has really kind of
6 blown up in the context of both media. It has now been
7 present in a number of actual medical media platforms,
8 but has now gone into actually the lay media. And it's
9 engendered actually a lot of discussion and debates
10 amongst oncologists and also clinical trialists.

11 And this is one of the hottest tickets at AACR.
12 Dave Hyman, who's a champion of precision oncology and
13 also basket studies versus, besides who's, who's I
14 think very thoughtful about these issues and is a critic
15 of these tissue agnostic indications.

16 And so the critics would argue, the critics
17 would argue that we are headed towards in some sense
18 the unknown and maybe even disaster. And people have
19 argued that, the critics have argued that we are
20 opening a Pandora's Box where we will explode not only
21 wrong therapies, but even budgets and medical costs.

22 So, I was asked to kind of try to frame this

1 issue of tissue agnostic therapy in the context of a
2 scientific frame and also what are the questions, what
3 are the issues in the context of clinical trials.

4 I don't, I think that you have to also include
5 here this issue of tumor biomarker agnostic biomarker
6 studies because you really cannot talk about a clinical
7 trial or the scientific rationale without that 'cause
8 we are in a way reclassifying a disease not based upon
9 histology, but really based upon a pathway or a marker.

10 So, Dr. Le is here and I'm not going to be able
11 to give justice to her research, but this is what
12 really set off this and opened this idea of, of tissue
13 agnostic therapy. And so I think this is a perfect
14 example as to how we can frame scientifically what we
15 should think about when we think about tumor agnostic
16 therapy.

17 And as you can see here, this landmark paper
18 showed significant activity in patients with MSI-high
19 tumors across histologies with anti-PD-L1 therapy, in
20 this case pembrolizumab.

21 And this, this was a culmination of data that
22 the FDA had accumulated from a number of keynote trials

1 showing that across histologies you had a number of
2 significant responses, but more importantly, these
3 responses were durable and there was clear clinical
4 benefit.

5 So, what is the scientific framework? And Dr.
6 Le gave a great lecture at this past ASCO on kind of
7 their hypothesis that brought about this investigator
8 initiated trial that eventually led to this approval.
9 And that really formed three thoughts, the scientific
10 basis of this. One was is that if you looked across
11 all these histologies, you saw these infiltrating PD-L1
12 positive CDA tumor cells, whether it was colorectal,
13 whether it was endometrial, whether it was gastric.

14 In addition, these mutation, this aberration
15 of the, of the mutational pathways led to multiple
16 mutations or high TMB or high tumor mutational burden,
17 which led to frameshift alterations leading to what are
18 called new antigens, therefore, leading to targets for
19 these anti-PD-1 therapy.

20 And so Steve -- sorry. Steve was there at
21 that lecture and gave kind of the, the background and
22 he'll go into more details about this, about what led

1 the FDA to look at from a scientific viewpoint why this
2 was approved and that these tumors across histology
3 shared same common pathological characteristics, but
4 more importantly, they shared similar molecular and
5 immunological characteristics, mutational load, and new
6 antigen burden, which eventually led, based, the
7 scientific basis for this approval.

8 But this story does not always carry across
9 all different kind of tumor agnostic ideas. One is
10 the story of BRAF. And many of you know that BRAF
11 inhibitors have already been improved in melanoma, but
12 the thought was that maybe since BRAF occurs in perhaps
13 most different, BRAF mutations occur at least, occurs
14 in most types of tumors, perhaps a tissue agnostic
15 indication is warranted.

16 However, when they tested this, particularly
17 in colorectal, we found that indeed this pathway was
18 not as similar to that in melanoma. In fact, elegant
19 research done by Prahallad, et al, and others
20 have shown that this pathway is different when you
21 inhibit it with a BRAF inhibitor. Vemurafenib induces an up-
22 regulation of this facile EGFR in colorectal.

1 And since then there have been other clinical
2 trials showing that perhaps in combination with EGFR
3 inhibitors such as cetuximab, plus other agents such as
4 irinotecan, which I have done with Dr. Kopetz can
5 overcome this lineage. But what BRAF, the story told
6 us was indeed lineage does matter in some instances.

7 Likewise, recently Dave Hyman reported this in
8 Nature, reported this at the last AACR in 2017 showing
9 that neratinib in blocking HER2 mutations depends
10 exquisitely on histology, does depend on lineage. And
11 if you look at this graph, it's not just one mutation
12 like in BRAF V600, but multiple alterations along that
13 HER2 gene looking at responses in different
14 histologies. You see that in different histologies
15 such as breast, you have exquisite response, but in
16 other tumor types such as bladder or colorectal,
17 there's almost no response to inhibition of this
18 pathway.

19 So, this story tells us that -- what these
20 examples tell is that definitely when we think about
21 tumor agnostic therapy, we need to have a scientific
22 framework, a hypothesis such as with pembrolizumab and

1 anti-PD-1, that may cross the threshold of histology
2 and lineage.

3 One question I think that comes up in all of
4 this is how many tumor types. How many tumor types do
5 we need to have before we consider a truly tumor
6 agnostic therapy? And I think that question is a much
7 more nuanced question that entails not just a
8 scientific question, but also a regulatory question.

9 This is an example of a trial that one of my
10 colleagues, Dr. Subbiah, recently reported at AACR,
11 and this is a RET inhibitor. And we saw exquisite
12 activity in a number of tumor types, lung, medullary
13 thyroid, papillary thyroid, but what he doesn't show
14 here is, is that they were one-off responses in
15 diseases even like pancreatic and cholangio.

16 So how many tumor types do we really need from
17 a scientific perspective to say that this, this
18 hypothesis kind of runs across the spectrum of
19 diseases?

20 So, let's talk a little bit about tumor
21 agnostic biomarkers. I think there are several
22 questions that we need to ask when we talk about tumor

1 agnostic, because again, reclassifying this disease as,
2 rather than based upon histology, rather by molecular
3 phenotype, and we do that by identifying a biomarker
4 that can identify that molecular immunological
5 phenotype. And the questions are, is this predictive
6 across lineage and histology?

7 Is this consistent and reliable across these
8 lineage in the cells, the actual test itself, and is
9 there a concordance in kind of in the real-life setting
10 both between labs and different types of tests that may
11 look for that?

12 And so, ideally we would like to have a
13 biomarker like Danielle Lei who's smart enough to set her,
14 her Girl Scout cookies right outside of a marijuana
15 dispensary in San Francisco, right? And is able to, to
16 capture all these customers. I want to remind us that
17 there are many different types of tumor agnostic
18 biomarkers, risk markers, diagnostic markers, activity
19 markers, and particularly when we talk about tumor
20 agnostic biomarkers in this setting, we're talking
21 about predictive markers.

22 And ASCO recently in 2006 had a definition of

1 what that is. It's a marker that identifies groups of
2 patients who receive different degrees of benefit. I
3 don't necessarily agree that you need to require a
4 randomized trial, but I do agree that association needs
5 to be specific to a given treatment, that it helps
6 maximize that benefit received from a given treatment,
7 and minimizes harm from treating patients, and that it
8 needs a test for interactions to determine whether a
9 treatment effect is different in patients who are both
10 positive or negative.

11 And obviously we, again, this case with MSI-
12 high, whether it's by PCR or IHC, suggests that this is
13 clearly a predictive marker of benefit from anti-PD-1
14 therapy. But there are other examples. One is a trial
15 that I've been involved in and NTRK fusion is right now
16 in the crosshairs of whether or not to be approved or
17 not.

18 And this shows it's a complex assay, whether
19 it's by FISH or NGS, but what we've seen is, is that in
20 every single patient who has an NTRK fusion, whether by
21 NGS or by FISH, we see an exquisite response and an
22 almost 80% response independent of histology,

1 independent of, of the fusion partner, independent of
2 age.

3 But, you know, assays and biomarker tests are
4 a complex thing and many of you guys who are involved
5 in that know this, and that even the history of ALK
6 fusion testing has undergone a number of different
7 reiterations over time. And one question is with, for
8 example, with, with pembro and MSI testing, is to what
9 extent are these two tests coherent.

10 And there's two ways to test for MSI-high
11 status. One is MSI PCR and the MMR IHC. In the
12 community, you know, pathologists will either order the
13 PCR or IHC, or sometimes ideally both, but there
14 are discordances between these tests. And Russell Broaddus
15 presented this at AACR, he's a pathologist
16 at our group at MD Anderson, and he argued really the most
17 accurate test is really to combine both a PCR and the IHC.

18 And you can see that there are some
19 discordances across different histologies, right? This
20 is a, a, this is a report that was published in 2002
21
22 all by, what they found was that, that these, the,

1 sorry, the MSI testing was much more accurate in
2 colorectal cancer relative to endometrial. So, what is
3 that threshold of accuracy? What is that threshold of
4 concordance that we would come to agree to as a, both
5 as an Agency and as a community?

6 Likewise, this is, this is test data from an
7 ongoing trial, a trial that a colleague of mine, Dr.
8 Mike Overman, looked at MSI status in colorectal
9 cancers in the nivo trial ongoing. And what they
10 showed was that there was a discrepancy between
11 different labs, and central labs versus local labs
12 showed a discordance of almost 20%. And what is that
13 threshold as both as an Agency and as a, and as a
14 community will we be willing to consider?

15 I think one interesting question that may come
16 up in the near future is this issue of kind of
17 threshold and tumor mutational burden, which MSI kind
18 of falls underneath, as you know, as I shared that MSI
19 patients have these very high tumor mutational burdens,
20 is likely going to be something that may come up as a
21 possible agnostic application. And that there have
22 been groups that showed that across different

1 histologies with PD-1 therapy, there can be benefit
2 based upon mutational burden irregardless of histology.

3 And most recently at AACR there was a data
4 presented on lungs showing that with nivo in ipi,
5 significant, significant benefit could be achieved in
6 patients with certain threshold of high tumor
7 mutational burden.

8 This is data from Dave Hyman and the MSK group
9 that showed a retrospective analysis of patients who
10 had, they looked at tumor mutational burden and benefit
11 from anti-PD-1 therapy across different histologies.
12 As you can see, there were a number of patients who
13 did, tumor types that did receive benefit. But as you
14 can see on the cutoff, there were different cutoffs as
15 to benefit.

16 So, what is that -- how do we design clinical
17 trials? How do we make indications where there are
18 different cutoffs in which a biomarker is either
19 positive or negative, since most of the tumor agnostic
20 trials, at least one, has really been a binary plus or
21 minus present biomarker?

22 My last section is on consideration of

1 clinical trials and I think there are three questions
2 that emerge from this. One is what is the best
3 endpoint when we design tumor agnostic clinical
4 trials? Second, what is the best trial design, and
5 lastly, are randomized clinical trials really needed in
6 this context?

7 This is the Phase 1 trial that Eunice Kwak ran
8 on ALK-positive, with crizotinib, ALK-positive non-
9 small cell lung cancer. And this trial obviously
10 showed incredible response in this subset of patients,
11 but led to an eventual randomized Phase 3 trial and led
12 to the approval of crizotinib in second line non-small
13 cell lung cancer. And clearly what it shows is that
14 response, even in an early setting, can be predictive
15 ultimately of approval and benefit.

16 And we've looked at that in our patient
17 population, which is primarily Phase 1 refractory
18 patient populations. We looked at close to 1,000
19 patients, did, did response ultimately lead to
20 correlation with survival and we showed that in this,
21 in this analysis that we did in 2015. But most of
22 these trials were specifically precision medicine or

1 targeted agents or cytotoxic agents.

2 But there have been others. Ritchie, et al, this
3 was a recent paper that was published in JAMA Oncology,
4 that showed that other therapies, such as
5 immunotherapy, may actually benefit from a different
6 surrogate marker like progression-free survival. This was
7 an analysis, a meta-analysis that was done showing that
8 six-month progression-free survival is actually a
9 better predictor of 12-month overall survival than
10 response rates in 25, comparing Phase 2 to 25
11 randomized immunotherapy trials.

12 So, what is the best trial design? To date the
13 trial design that people have most used are what are
14 called basket trails where you have different
15 histologies targeting one certain pathway. And that's
16 contrast from what are called umbrella trials, which
17 you have one type of cancer and different genetic
18 mutations testing multiple different drugs.

19 And this is one of the basket studies that has
20 been highlighted recently, both in the New England
21 Journal and number, and has led to a number of recent
22 Approvals, led by Dave Hyman at MSKCC. As you can see,

1 this was a trial where they targeted the BRAF V600
2 gene, allocated a number of different histologies and
3 tumor types, and what they found from the study was, is
4 that indeed there was significant activity in different
5 histologies, right? Non-small cell lung cancer showed
6 significant activity, which eventually led to further
7 studies in the Rohr study showing significant activity.

8 Also in anaplastic, which recently achieved
9 approval. The most, and also Erdheim-Chester, which is
10 a rare type of lymphoid malignancy which shows
11 incredible activity with this basket trial.

12 But there are critics who say that these
13 basket trials are underpowered. They have problems
14 with prognostic heterogeneity, etc. And some people
15 argue, Don Berry and Brian Hobbs at our group, our
16 Bayesian statistician, argue that there are ways to
17 improve this. Adaptive enrichment designs have been
18 used in umbrella studies such as I-SPY and BATTLE to
19 really powerful effects. And one can use Bayesian
20 basket trial designs with what are called hierarchical
21 modeling based on exchangeability.

22 I'm not going to try to explain this in a

1 nutshell here, but essentially the idea is, is that
2 using Bayesian statistics you can actually group these
3 different arms showing better sensitivity and
4 specificity and true effect across these different
5 histologies.

6 The last question is do we need a randomized
7 clinical trial? And I would argue to you not
8 necessarily. And in fact, I would say that for rare
9 tumors and orphan diseases, it is almost impossible, if
10 not impractical. And in fact, the FDA history would
11 suggest that the test of time does show that randomized
12 clinical trials are not always necessary.

13 This was an analysis that we did of all FDA
14 approvals from 1973 in Oncology through 2006, over 68
15 drugs. Thirty-one of those drugs were conducted
16 without a randomized clinical trial. And if you looked
17 past that, many, many years past that, only one of
18 these drugs after post-market approval were rescinded,
19 gefitinib, and many of these went on to get further
20 additional uses. Nineteen of the thirty-one went on to
21 additional uses. So therefore, and to some extent the
22 test of time showed that randomized clinical trials are

1 not always necessary.

2 And these are just some of the most recent
3 approvals that are based upon nonrandomized clinical
4 trials. And as you can see, both progression-free
5 survival shows that maybe there are, there's clinical
6 benefit and we'll see what the test of time is in the
7 context of the kind of post-market. But we'll see. But
8 I suspect that these two will move on and show true
9 benefit.

10 I want to remind us that as Steve has
11 mentioned in, in his past lectures, that, you know,
12 approval is not necessarily a clinical trial, right?
13 That I think the FDA has had really kind of
14 thoughtfulness and forward-thinking in the context
15 that, you know, you really kind of look at the, the
16 weight of the full evidence.

17 And this is the case, for example, in not only
18 in pembrolizumab, but also in our NTRK application,
19 larotrectinib application, where we've really, the
20 FDA's really taken into consideration three different
21 trials, both the Phase 1 and the Phase 2 adult, which I
22 helped run, and also the pediatric Phase 1 to kind of

1 bring back together the, the cumulative data and this
2 rare subset of patients.

3 So that is the end of my talk. I want to
4 thank all my colleagues who helped me bounce a lot of
5 ideas, and also many of the people here who I stole
6 slides from. And thank you very much.

7 (Applause)

8 DR. SUL: Thank you, Dr. Hong. So, with
9 that background information on the scientific rationale
10 for considering tissue agnostic drug development in
11 oncology, our next speaker, Dr. Steven Lemery, will
12 talk a little bit about the regulatory perspectives.
13 Dr. Lemery is an Associate Director in the Division of
14 Oncology Products 2 in the Office of Hematology
15 Oncology Products. He also led the team that reviewed
16 the MSI-high application for pembrolizumab for solid
17 tumors. So, he's, you know, what I consider our office
18 expert in this area. So welcome to Dr. Lemery.

19 PRESENTATION - OFFICE OF HEMATOLOGY AND ONCOLOGY
20 PRODUCTS (OHOP) PERSPECTIVE

21 DR. LEMERY: Thanks, Joohee. So, the first
22 part of my talk will, will cover some, much of the same

1 information that, that David covered. But the second
2 half sort of really switches onto what the purpose of
3 the, of the meeting here is today. So as has basically
4 been mentioned, traditional development paradigm has
5 been based on a single tumor type or a biomarker in
6 that tumor type. For example, previously untreated
7 pancreatic cancer or HER2 positive breast or gastric
8 cancer.

9 So, I'll briefly touch base about the, the case
10 study of pembrolizumab, which David also talked about.
11 This is very, very, very simplistic. So, for anyone
12 who's a true scientist in this field, you know, this is
13 simplistic, but mixed matched deficiency is caused by,
14 generally caused by, mutation in the one of four DNA
15 repair proteins. It could be the result of Lynch
16 syndrome, which is a cancer predisposition syndrome, or
17 a somatic mutation of one of these four proteins.

18 It can also be related to inactivation of, of
19 DNA that inactivates one of these four proteins, and
20 especially in colon cancer that's probably the more
21 common cause of mismatch repair deficiency and it's
22 usually diagnosed with immunohistochemistry.

1 Again, this is simplistic. The microsatellite
2 instability is in essence the phenotype of deficient
3 mismatch repair. Microsatellites are, are pieces of
4 DNA that are short repeats. Their lengths are variable
5 from person to person. And if someone has
6 microsatellite instability, this can be detected
7 through either PCR or next generation sequencing.

8 So, for the Keytruda, pembrolizumab, approval
9 microsatellite instability or deficient mismatched
10 repair, not the organ, defined the indication. And
11 this'll be important subsequently when I'll talk a
12 little bit about indications versus disease.

13 Here's a slide that talk, that shows the
14 prevalence of microsatellite instability in different
15 tumor types that was shown in one paper. And of note,
16 the, the second one -- some of these are more common
17 tumors than others. The second bar is COAD, is colon
18 cancer, and I think READ is rectal cancer. So those
19 are more prevalent cancers. And so when you take the
20 prevalence of MSI and colon cancer, it probably would
21 not meet the threshold for orphan status, which is
22 200,000.

1 Some of these, though, like for, for example,
2 neuroendocrine tumors, they're, they're very rare tumors and
3 when you take a subset of them that are microsatellite
4 instable, it makes an extremely rare tumor. So, some
5 of these tumor types are extremely rare. And even when
6 you look at colon cancer, this is the, the incidence
7 and, or prevalence in all-comer patients in the
8 metastatic setting, which pembrolizumab was approved
9 for. It's a much more rare -- it's, it's less common.

10 So why does having deficient mismatch
11 repair MSI matter? So as David mentioned, the, this
12 causes a greatly increased number of mutations in
13 tumors. Some of these mutations may be targeted by the
14 immune system and pembrolizumab can facilitate an
15 immune system response in some of those cancers.

16 So, this was a cartoon that basically shows the
17 mechanism of action. So again, you have these
18 increased number of mutations. Increases the
19 probability that you'll have a neoantigen, which the T
20 cell can respond to. However, the, you know, cancers
21 have a clever way of, of preventing this immune attack
22 and one of them is through the PD-L1 system. So

1 pembrolizumab can block PD-L1 and result in an immune
2 attack against the tumor cell.

3 So as was stated earlier, this is the data
4 supporting the approval. So, a response rate of, of, I
5 think about 39% all-comers. And, you know, there may
6 be differences in some of the tumor types in the
7 qualitative response rates. You know, again, some of
8 these patients have received different, different
9 numbers of, of chemotherapy. Their immune systems may
10 be different. So that may explain some differences in,
11 in response rates across tumors. However, we didn't
12 really observe a, sorry, a qualitative difference, but
13 there may be slight quantitative differences.

14 What was really impressive is that these
15 responses appeared very durable. This is in contrast
16 to what you, what we've historically seen with
17 cytotoxic chemotherapy where responses last in the
18 order of, you know, a couple months.

19 Also of note for this -- this is biomarker-
20 directed development. So, in colon cancer in Dr. Le's
21 initial study, none of the patients with microsatellite
22 stable tumors responded. You know, this shows that in,

1 at least in colon cancer that MSI did appear to be an
2 important biomarker for selection of, of benefit.

3 There's also limited activity of immunotherapy
4 as single agents in many microsatellite stable, quote,
5 unquote, "cold tumors." So, you know, pancreatic
6 cancer, we haven't seen a lot of activity with
7 different checkpoint inhibitors in, in this tumor.

8 There are responses in certain other tumors
9 that are microsatellite stable, what we call hot
10 tumors. These are, include lung cancer, melanoma, and
11 these patients often have high mutation burdens. Their
12 tumors have high mutation burdens due to other reasons,
13 smoking in lung cancer, or UV exposure in melanoma.

14 So as was mentioned, we thought there was a
15 strong scientific biological rationale. We thought
16 there was compelling clinical data. And there's been a
17 favorable risk/benefit profile of pembrolizumab with
18 similar response rates in other indications that were
19 studied. So for example, melanoma has a high response
20 rate, a similar response rate, and had a favorable
21 risk/benefit in randomized trials, you know, and lung
22 cancer as well.

1 So although, although tissue agnostic approval
2 has been granted, tissue agnostic approvals may not be
3 appropriate for all targets. And David mentioned the,
4 the BRAF example. So it's as single agents or, or as,
5 as double agents of BRAF/MEK inhibitor alone, there, they've
6 shown to be effective in BRAF mutant melanoma, non-
7 small cell lung cancer, anaplastic thyroid cancer, and
8 as a single agent, vemurafenib, has been approved for
9 Erdheim-Chester disease. However, as a signal agent or
10 as a, as two agents together, they're less effective
11 for BRAF mutant colorectal cancer.

12 It should be noted, though, that knowledge of
13 these effects in melanoma where randomized trials had
14 been conducted, have facilitated approvals based on
15 very small trials and some of these other indications.
16 So we approved anaplastic thyroid cancer. It was based
17 on fewer than 30 patients. Same thing for Erdheim-
18 Chester disease. And, you know, we saw very high
19 response rates in these, these tumor types.

20 Anaplastic thyroid cancer is, is a devastating
21 cancer. We saw a response rate that was similar to
22 melanoma. The response duration was similar to

1 melanoma. So we felt it was, it was, you know, these
2 patients have the highest of unmet medical need. It
3 takes, you know, these are really, really rare tumors.
4 It took, I think, over four years to enroll about 23 to
5 26 patients that have anaplastic thyroid cancer. So, we
6 thought it was appropriate to approve in that setting.

7 So we, when we granted the approval of
8 pembrolizumab, the, the question can be asked is was
9 the approval for a disease or an indication that
10 included many diseases? So, this is sort of
11 what the, what we're getting here today. So as, in OND
12 we, we approve an indication in essence which could be
13 for either of these two scenarios; however, orphan
14 drugs are approved for diseases.

15 The only, interestingly, the only place when I
16 did my talk at ASCO last year that I found a definition
17 of the disease was in the food regulations. And this
18 sort of, it didn't really apply to, you know, the
19 setting that we're talking about today. So damage to
20 an organ, part, structure, system of the body such that
21 it does not function properly. Or a state of health
22 leading to such dysfunctioning. And this was to

1 differentiate supplements versus a drug.

2 So how should disease be defined? Should we
3 define by indication, quote, unquote, "MSI-positive
4 cancers" which is, you know, lumping, or by splitting?
5 Do we, do we define disease as cholangiocarcinoma,
6 microsatellite unstable cholangiocarcinoma,
7 microsatellite stable cholangiocarcinoma? And you can
8 go really, you know, you can really keep splitting and
9 splitting and splitting.

10 So, arguments against splitting for the MSI
11 example that we approved. So, many microsatellite
12 unstable cancers share common histological
13 characteristics. So many, you see lymphocytic
14 infiltration. You see medullary type patterns. A
15 misspelling there. And microsatellite tumor share
16 increased mutation burden and a response to checkpoint
17 inhibition.

18 However, you can make an argument against
19 splitting. I'm sorry, for splitting. So mismatched
20 repair deficiency or microsatellite instability is not
21 the only molecular finding in patients. Other driver
22 aberrations may differ in different cancers. There may

1 be differences in the natural history of some of these
2 patients with different cancer types. So, for example,
3 FOLFOX is a commonly used regimen for colorectal
4 cancer. Would that be effective to treat patients with
5 glioblastoma? Probably not.

6 And I'll, I'll briefly mention NTRK in a few
7 slides, not the, simply as a, as a disease entity. So
8 an NTRK fusion-positive child with infantile
9 fibrosarcoma is not going to be the same as a disease
10 of the NTRK fusion-positive non-small cell lung cancer.
11 You know, however, should we split ad infinitum? You
12 know, you can make the case whether we get -- you know,
13 you can make an almost infinite number of orphan drug
14 requests if we keep splitting.

15 Other splitting considerations. So maybe
16 company, you know, we have, we've approved
17 pembrolizumab for, for tissue agnostic MSI indication.
18 Company B may not, may not pursue a tissue agnostic
19 indication. So an example of this is nivolumab was
20 approved for a microsatellite instability high
21 colorectal cancer based on data on patients with
22 colorectal cancer.

1 As I stated, this may, MSI colorectal cancer
2 may not be orphan, may not have met the criteria for
3 orphan status, but maybe MSI-positive endometrial
4 cancer or neuroendocrine tumors could have. You can
5 see how this could be a situation where companies could
6 try to, you know, you know, game the system in essence.
7 And so we have to really think these, these scenarios
8 carefully.

9 You know, there, there's a benefit of orphan
10 development, orphan status where, you know, we're
11 trying to encourage development in rare diseases, but,
12 you know, there's also the, the flip side where you
13 want competition in the market. These are expensive
14 drugs.

15 You know, and I have the second bullet, is
16 what are the effects of orphan drug designation if
17 Company B or C requests orphan status for MSI
18 cholangiocarcinoma? Maybe this differs if it's a PD-1
19 inhibitor, or versus a small molecule that doesn't
20 target that biomarker. You know, when should a tissue
21 agnostic orphan designation be granted?

22 You know, historically we've done it at any

1 time, but, you know, should it be early? Should it be
2 late? When we have sort of sufficient information that
3 this is likely to be a tissue agnostic pathway? These
4 are some of the questions we'll discuss today.

5 So as was mentioned, orphan drug designation
6 has been granted for NTRK fusion-positive cancers. In
7 toto, in toto the FDA felt that this met the, the
8 criteria. You know, and, you know, as a question does
9 it make sense -- would it make sense to have separate
10 designations for an enumerable number of NTRK fusion-
11 positive cancers?

12 So I think in the, in the New England paper, I
13 think that were 12 cancers listed. Put that with an
14 additional factor of they're different NTRK fusion
15 proteins, and then over 10 different fusion partners.
16 And as you can see, if you mix and match them all
17 together and submit a separate request for each one,
18 you know, you can almost, you know, go infinite number
19 of applications.

20 How will tissue agnostic approval impact
21 development for biomarker negative populations? This
22 is one that we're going to have to think about policy wise

1 as an, as an Agency. So, should MSI patients be
2 excluded from clinical trials of single agent PD-1
3 inhibitors? If not, how to assess whether an effect is
4 driven solely by the biomarker. At a minimum, the
5 biomarker should be identified in these trials.

6 And as a hypothetical example, you know, if
7 you have a, if you have a drug that has a 40% response
8 rate, how do you consider randomized trials in, in non-
9 biomarker selected patients, you know? It may differ
10 depending on what the response rate is in
11 microsatellite stable patients. Is it 1%? Five
12 percent? Ten percent?

13 Also, what is the incidence of prevalence in
14 that cancer type, which, you know, if the, if it's super
15 rare, if the prevalence of a biomarker's super rare in
16 that cancer type, 1%, it may not matter if you're
17 measuring that biomarker in the rest of the patients.

18 How will tissue agnostic approval impact
19 development for biomarker negative populations? Again,
20 it's taking on the prior slide. What if the
21 investigational drug is a cytotoxic or a multitarget
22 TKI? Presence of MSI may not matter. Again, these are

1 scientific questions, but what about orphan disease
2 designation which is, which is what we're taking about
3 today?

4 So in summary, tissue agnostic approvals is a
5 potential pathway for approvals if scientifically
6 justified. Tissue agnostic orphan drug disease
7 designations have been granted, but there are
8 challenges once a, once a designation is granted. You
9 know, what about requests from another company for a non-
10 tissue agnostic indication with the same biomarker?
11 What if it's the same pathway? What if it's a different
12 pathway?

13 There's going to be a lot of sort of scenarios
14 I think that we're going to go through today and, and,
15 you know, I think everyone will see it's going to be a
16 challenge to, to just, to go through.

17 (Applause)

18
19 PRESENTATION - OFFICE OF ORPHAN PRODUCTS DEVELOPMENT

20 (OOPD) PERSPECTIVE

21 DR. LEWIS: Thank you, Steve. I really
22 appreciate this transition that we're making where
we're talking first with Dr. Hong's presentation on the

1 science, on these issues to ground us there, and then
2 as we move to the questions that are really in our
3 focus today, which is about orphan drug designation in
4 this context and also our exclusivity.

5 So, we knew it was important to talk a little
6 bit about our orphan drug framework for designation and
7 exclusivity. And so I'm going to do a, as you said,
8 kind of a simplistic look at how these elements work
9 together, but I think it's critical as we talk about
10 this in our discussion a little bit later today.

11 So, if I can go to the next slide. The goals
12 that we have in this part of our program is to give you
13 this overview. You'll learn a little bit about
14 designation. Many of you know it closely, so please
15 bear with us. And then we'll talk a little bit about
16 our exclusivity framework and how that works. We'll
17 provide that context of these, these issues with the
18 tissue agnostic elements that we've talked about today
19 already.

20 We'll even talk a little bit about diseases
21 and conditions and indications, and we'll introduce
22 some of these issues that are so relevant as we go

1 forward.

2 So, many of you are familiar with the Orphan
3 Drug Act. It facilitates the development of drugs for
4 rare diseases. It provides financial incentives that
5 are going to reduce the costs of development. And the
6 idea is that there are rewards then to these sponsors.
7 Some come right with designation and some come only to
8 the first successful sponsor for a seven-year marketing
9 exclusivity.

10 This Act, the Orphan Drug Act, first came
11 about in 1983, but it's been amended a number of times
12 and most recently just with the Reauthorization Act in
13 2017. We've also issued regulations and they help us
14 implement; they help us safeguard and protect those
15 incentives to be sure that we're doing things properly
16 as we designate and as we provide exclusivity. And
17 I've given that citation here for you, 21 CFR 316, that
18 will go through those elements.

19 So, when we do designate, we're designating
20 for, by our law and our regulations, for a rare disease
21 or condition. And so you saw Steve struggling a bit
22 with, you know, what definition should we be using on

1 disease as we go forward. But I want to share what's
2 in our, our law right now.

3 There's two parts to it. There's one part
4 that we're going to focus on and one we won't. The A
5 there, we're going to focus on the part of the
6 definition that it affects diseases that are affecting
7 fewer than 200,000 persons in the United States. And
8 that's really what our topic will be today.

9 There is another provision. It's not used
10 frequently. In fact, only three times in our history,
11 where a sponsor's able to show that they have a disease
12 that affects over 200,000, but the sponsor would be
13 unable to recoup their costs of development.

14 So, I'm going to set that aside for a little
15 bit and just go to one other aspect that has to be part
16 of the designation, and that's that the drug must show some
17 promise for the prevention, diagnosis, or treatment of
18 that rare condition or rare disease.

19 So, you may be wondering, well, wait a minute,
20 I've heard about orphan subsets. What is that? You
21 know, you just told me that we deal with things under
22 200,000. In our regulation, there is a provision

1 called the orphan subset and it's defined there and I
2 give that citation to you.

3 A rare subset of persons within a common
4 disease, what does that mean? And many people
5 misinterpret this and miss, and I don't know it'll be a
6 big element today, but I'm going to include it because a
7 little bit of completeness in case this comes up.

8 So, if you have a rare subset of persons with a
9 disease that's not rare, but the use of that drug could
10 only be used within that subset, that is where we're
11 going to be talking about right now.

12 I'm saying that if you take a common disease,
13 we always, always when we do designation we pair
14 together the drug and the condition. And when you look
15 at that, you look at that mechanism and how it works,
16 and you have to be certain that either through some
17 aspect, some property of that drug, would not be
18 appropriate to use outside that subset.

19 So, could be because of toxicity. That's a
20 thing that happens where you would only be able to use
21 this very toxic drug within the subset. It could be
22 the mechanism of action is such that it would only be

1 useful in this orphan subset. Or it might even be
2 clinical experience that shows it does not work
3 outside, across the whole disease.

4 So, these are very unusual circumstances. A
5 lot of people think we have subsets often, but it's
6 not. It is not a common thing and we, this definition
7 will still safeguard the Orphan Drug Act intent. It
8 prevents misuse from people who sometimes think that
9 this is dividing a disease inappropriately.

10 So, I'm going to move from subsets and really
11 from designation for a moment and talk about
12 exclusivity. And I'm skipping a lot of things. What
13 happens when you get designated? There are certain
14 incentives you get. You get tax credits reduced now to
15 25%, but you also get a waiver of user fee for the
16 application. But I'm going to skip now to exclusivity
17 because that's our other topic we want to talk about
18 today.

19 An orphan exclusivity provides seven years of
20 marketing exclusivity to that first sponsor that
21 successfully gets that indication for, and specifically
22 that indication. It will mean FDA cannot approve that

1 same drug for that same indication for seven years.

2 And I have a few points I would like to make about
3 that.

4 That is that, the drug is actually, usually
5 approved for an indication that's within the whole
6 orphan drug designation. We will designate a whole
7 disease, and I'll talk in a moment to you that the
8 exclusivity comes to the approved indication alone.

9 That, it's also important, that that same drug
10 has not been previously approved for that same
11 indication. So, it's not that everybody comes along
12 with a designation will get exclusivity. We'll always
13 look to see if the same drug has been approved for that
14 same indication in the past.

15 And I'll also talk in a moment about a part of
16 the framework that tries to balance protecting the
17 exclusivity with providing patients with a superior
18 product when that's necessary. So, if a superior,
19 clinically superior product come along, you'll see it
20 won't actually be blocked from market by that
21 exclusivity.

22 So, right now we, we've focused a little bit.

1 We're going to be talking a lot about how to designate
2 and we'll designate for the disease. We, we want to
3 focus just for a moment on disease versus indication.
4 In the Orphan Drug Act, FDA grants this designation for
5 rare diseases and conditions. So, we'll be talking
6 about diseases.

7 But FDA when they do a marketing approval,
8 they approve something for an indication, which is
9 generally, as I said earlier, a little narrower in most
10 cases than the designation was. And I'm going to give
11 a couple of examples because I think it'll be helpful
12 to you.

13 The first example on, on the left is that we
14 might designate for mantle cell lymphoma and that's,
15 that's a rare condition. Not -- we aren't going for a
16 particular indication there. But once a product gets
17 approved, it might be approved for a much more narrow
18 indication. And the example here is the treatment of
19 adult patients with mantle cell lymphoma who've
20 received at least one prior therapy. So, you'll see in
21 a moment that's the indication we'll give exclusivity
22 for even though the designation is broader.

1 And there's a second example for you on this
2 slide. It's about designation for sickle cell. We may
3 designate the entire disease for sickle cell, but when
4 it comes to market the approved indication, maybe to
5 reduce acute complications of sickle cell in adults and
6 pediatric patients five years age and older. So
7 we'll have to deal with that indication when we look at
8 the exclusivity determination. That is where we'll be
9 giving exclusivity and it's narrowly protected only for
10 that approved indication.

11 So, what's the implication that, why am I
12 making such a big point about the disease versus
13 implication? Well, oftentimes we'll read in the
14 literature people who haven't made that distinction and
15 it might misguide them when they talk about this. So
16 we find that the way this works, we're reserving the
17 designation for the rare disease, but the exclusivity
18 is very limited to the approved narrow indication.

19 So that means the products can come to market
20 which are not within the narrow indication. It's, and
21 a subsequent sponsor can seek that, that drug for also
22 a different indication within the same disease or a

1 different disease altogether. So, understanding how
2 that works will help when you're reading other material
3 and help in our discussion today.

4 So, we've got a diagram of this. This is how
5 important this is for us, that we have a scope of
6 exclusivity from mantle cell and you can see that was
7 our designation in the whole blue circle, is to
8 represent the whole disease. And then when we have an
9 approval for the indication of patients with mantle
10 cell that received at least one prior therapy, that red
11 circle there is what is protected under exclusivity.
12 Not the rest of the disease blot.

13 And then similarly if you have a second
14 indication that comes along for the treatment of
15 patients who receive no prior therapy, that's a
16 different population. They may receive exclusivity
17 just for that narrow group there. And so you can see
18 not everything is protected by the indication. So, it's
19 worth understanding because of the confusion we
20 sometimes see in the literature.

21 So, I mentioned that, let's say I wanted to
22 Seek, I'm a sponsor and I want to seek designation
or exclusivity for the same drug that was already approved

1 for that same indication. Can I do that? Well, not
2 normally, no. Once something is approved, you are, we
3 are not going to designate it again, and we're not
4 going to then be giving it the, the various incentives
5 for the development.

6 But if the sponsor can provide a plausible
7 hypothesis of clinical superiority at the time of
8 designation, we'll evaluate that, and if it is an
9 appropriate plausible hypothesis of clinical
10 superiority, then we will consider it different and we
11 will designate, the idea being balancing that framework
12 of getting superior products to patients with rare
13 conditions.

14 But what happens then if they continue on to
15 approval? Will they automatically get exclusivity?
16 No. They have to demonstrate that there's a clinical
17 superiority finding in their, in their data. What kind
18 of clinical superiority do we mean? There is a
19 definition and the citation's there for you.

20 It means that that product is more safe or
21
22 more effective, or it's going to provide a major

1 contribution to patient care. And that's in unusual
2 cases that we go there. Generally we're looking for
3 greater safety and greater effectiveness. I don't know
4 that this will be a big topic today, but it's worth
5 touching on now.

6 So, what will be a big topic today? The big
7 topic for us comes as we're moving historically from
8 looking at anatomically based or histology based
9 cancers. As you heard already, that has been the
10 tradition that we expected studies for each individual
11 anatomical or each specific cancer. So Orphan Products
12 will align its incentives to what the expectation is
13 with, within the development paradigm.

14 So that was, that was working well until we
15 came to a point of now we see the questions that are
16 based on specific molecular markers. We ran into this
17 earlier in our program. As we would see in orphan
18 subsets, we would see, all right, we had non-small cell
19 lung cancer, which is not rare, but then there were
20 particular markers that even when you added those
21 markers together still were under the 200,000. It
22 wouldn't be expected to work outside that group. So

1 therefore, we began in this process to, to have a
2 subset, an orphan subset for specific molecular
3 markers.

4 And now we've gone further down this line that
5 for purposes of orphan designation and consider, and
6 that consideration, as well as, as we're moving to
7 exclusivity, we have to recognize that now there are
8 two tissue agnostic diseases or conditions, as we call
9 them. You'll see throughout our talk today we'll
10 probably be, are we talking, are we diseases, are we
11 talking indications. But the two, the two groups that
12 were considered were the MSI-high and the NTRK fusion-
13 positive.

14 Within MSI-high when you added all the groups
15 together, there were too many. You can't qualify for
16 orphan drug designation on MSI-high because the
17 prevalence over 200,000. But in the NTRK fusion-
18 positive, even when you added all the groups together,
19 it was under our 200,000, and that's why we have two
20 current designations for NTRK. And as you heard
21 earlier from the Commissioner, we also have one in
22 ophthalmology.

1 So, it's not that we think that this tissue
2 agnostic or agnostic situations are confined to
3 oncology. Oncology's in the frontlines of considering
4 these things, but it's going to be an issue across
5 diseases. Today we're focused on oncology.

6 So, these sort of principles that have evolved
7 but we want to discuss today, is that we, we considered
8 the prevalence, this cumulative count of all the
9 relevant cancers within a particular marker. And as
10 you saw, if it was over 200,000 we did not think we
11 should subset. Once that decision is made, we did not
12 think we could continue to subset individual cancers.

13 But then we became aware it's not as simple
14 as, as it first seems. For example, with MSI-high,
15 that was over 200,000 and it couldn't receive
16 designation for MSI-high gastric cancer. But what
17 about those that are not MSI-high? How do we, how do
18 we deal with those? Those will be questions that we
19 hope our panel can help address.

20 So is it possible that you may receive
21 designation for that rare gastric cancer, you should
22 if the drug works out the MSI-high target in gastric

1 cancer?

2 So, we have questions about overlapping or
3 different diseases. Can a tissue agnostic disease
4 overlap with the histology-specific disease? Should
5 they be considered completely separate? The example
6 that I'm providing here was the one we've seen case
7 studies for, pembrolizumab, which was approved for the
8 MSI-high tumors, but it's also approved for gastric
9 cancer. Where the populations overlap, what are these
10 implications for us?

11 We've talked within our groups, within our
12 workgroups, and today we'll be talking within our panel
13 and audience about designation, approval and
14 exclusivity, mainly really designation and exclusivity.

15 So, one of the considerations really important,
16 that people need to keep in mind, is that a lot of what
17 we've been looking at is a retrospective kind of look
18 at what, what we know how about these cases. But for
19 us the timing is really critical because sponsors seek
20 designation very early in development. So, a drug may
21 be designated for a histology-specific cancer, but then
22 after development it may turn out that over time it's

1 later approved for a tissue agnostic indication.

2 We have to think about previous approvals and
3 how that might impact our designation and our current
4 approvals. We've tried to develop some predetermined
5 scenarios that we'll be talking about in our panel.
6 They might be tough to, to stay on track, but hopefully
7 we'll be able to discuss some of these scenarios and
8 get some great input.

9 We know that there are difficult situations
10 that we may not be able to fully cover today. We know
11 that tissue agnostics are going to be involved in
12 combination therapies. We know that the testing is
13 important, that genome profiling for trials may be
14 relevant. We've not seen really a difference in
15 the pediatric aspects of tissue agnostic development, but
16 there may be discussion on that as well.

17 So in summary, this is just a quick overview,
18 but I, we think it's important because that's really
19 our topic. So understanding the context of designation
20 and how that works, and the exclusivity and how that
21 works, is critical to be able to discuss the topic.
22 We've given a little bit of context for designation and

1 introduced some of these issues for orphan drug
2 exclusivity and designation.

3 What I think I'd like to do now is just to
4 remind people that as we're going to be going on break
5 and coming back and our panel's going to go to work. I
6 want to let you know Joohee Sul, Dr. Sul, is going to
7 co-moderate this panel. You saw her a moment ago when
8 she introduced Steve Lemery. We've worked together in
9 a great way where she's done a detail with our group,
10 so has a little bit of experience, and so hopefully
11 between us we can keep track on the discussion.

12 Keep in mind during the discussion, these
13 questions, we'll be using these to help develop a
14 guidance document on this topic. And so we'll be using
15 the input we receive from the public today and working
16 to incorporate that into a guidance. So that's what
17 we're looking for today. That's our goal of the whole
18 program, a broad input on these topics.

19 I thank everyone up to this section, I think
20 we're going to go on a break now, and then after our
21 break we'll be set for our panel discussion. We'll
22 introduce our panel. In the meantime, everyone enjoy break and

1 we'll reconvene at 11. Is that right? Eleven o'clock.

2 Okay. Thank you, everyone.

3 BREAK

4 PANEL DISCUSSION WITH AUDIENCE Q&A

5 DR. SUL: The panel discussion, if everyone
6 can take their seats. Everyone, everyone standing, if
7 you could please take your seats so we can get started.

8 So, we're going to start our, our panel
9 discussion and this will be essentially to discuss some
10 of the scenarios and the topics and the issues that
11 were brought up by the speakers in their presentations
12 this morning. And really to get a sense of, you know,
13 what the Office of Orphan Products is, is facing when
14 they're looking at both designation and exclusivity
15 issues related to the tissue agnostic drug development
16 that's going on in oncology.

17 So before we begin, it's always kind of nice
18 to know who's in the audience. So I've, just curious
19 who from the audience is from industry? Could you show,
20 raise your hands? Okay. A lot. Which is, which is I
21 think what we kind of expected. What about from
22 patient advocacy? Great. Academics? Government?

1 There's probably a lot of us here. Yeah. Anybody I'm
2 missing? Oh, yeah, press. Okay. Great.

3 And I think what, the way we'll start, the way
4 we'll start the panel is first we'll have our panelists
5 introduce themselves and say a little bit about what
6 their interest is in tissue agnostic drug development
7 because some of our panelists didn't get a chance to,
8 to speak. And then we'll move on to get some
9 clarifying questions, particularly if there are questions
10 related to the orphan drug designation process and
11 exclusivity. And then we'll move on to the questions
12 that are included with the workshop.

13 So we'll start at one end. Just to let
14 everybody know on the panel that when you go to speak,
15 you should press the button on the mic and wait for the
16 red light. That's how you know that you're going to be
17 heard.

18 MR. KARST: Great. My name is Kurt Karst.
19 I'm from Hyman, Phelps & McNamara here on behalf of the
20 Association for Accessible Medicines. And I certainly
21 have a significant interest in the Orphan Drug Act. I
22 work with numerous companies whether generics or brands

1 on designation and exclusivity issues. Probably have
2 worked on 100, 200 designations over the years.

3 MS. SHER: My name's Rachel Sher. I'm deputy
4 general counsel at the Association for Accessible
5 Medicines. And we represent the manufacturers of
6 generic drugs, small molecule, traditional generic
7 drugs and biosimilars.

8 And obviously our interest in being here today
9 is to discuss issues around exclusivity and sort of the
10 appropriate scope of exclusivity when we're talking
11 about tissue agnostic therapies that, that strikes the
12 right balance between ensuring that there are
13 appropriate incentives for innovation on the one hand
14 and opportunities for generic and biosimilar
15 competition at the expiry of that
16 exclusivity period. So, thanks for having us.

17 DR. STEWART: Hi. My name's Mark Stewart.
18 I'm here on behalf of Friends of Cancer Research. Our
19 organization's been closely involved in much of the
20 discussions around drug regulatory policy with the goal
21 of ensuring patients have access to innovative
22 therapies as safely and quickly as possible.

1 And our interest in this is multifaceted both
2 on the science side in terms of the scientific
3 justification and requirements around receiving a
4 tissue agnostic approval.

5 And then also both on what makes sense for the
6 patients in ensuring that patients have access to
7 drugs, particularly with these agnostic approvals that
8 often rely on diagnostic testing and making sure that
9 the diagnostic tests are appropriately available and
10 have the appropriate testing and methodology in place
11 to ensure that patients are assigned to the correct
12 drug.

13 DR. LE: My name's Dung Le. I'm a GI medical
14 oncologist at Hopkins and I run clinical trials. And I
15 helped design and implement the very first trial
16 looking at pembrolizumab in a tissue agnostic manner.

17 DR. MELLIS: Hello. My name is Scott Mellis.
18 I'm a rheumatologist. I work at Regeneron
19 Pharmaceuticals, a biotechnology company in New York.
20 And we're very interested in science-based drug discovery
21 and development. And with our focus on targeted
22 therapeutics, it becomes clear that tissue agnostic

1 approaches to drug development are rational, both in
2 the oncology area, as well as the non-oncology areas.
3 So, honored to be able to participate in this
4 discussion. Thank you.

5 DR. STARTZMAN: Hi. I'm Henry Startzman.
6 I'm, I direct the Orphan Drug Designation Program in
7 the Office of Orphan Products Development.

8 DR. LEWIS: I'm Debra Lewis, Acting Director
9 for Orphan Products Development. And serving as co-
10 moderator with Joohee.

11 DR. HONG: I'm Dave Hong. I'm at MD Anderson
12 Cancer Center. I'm an oncologist that does really
13 early drug development there. And I guess my interest
14 is, is that you, not only do I do these clinical
15 trials, but a lot of my patients are now coming in
16 with, you know, tumor markers, molecular tumor markers
17 asking for new drugs that target their specific
18 pathways. And so, and we're seeing actual real, real
19 evidence of benefit in these patients.

20 DR. LEWIS: I'm getting the word from our tech
21 people. In order for people online to hear, we
22 actually have to be uncomfortably close to these

1 microphones for, for people on the webcast to
2 understand us, even though we can hear in the room.

3 DR. KUMMAR: I'm Shivaani Kummar. I'm a
4 medical oncologist and I run the Phase 1 clinical
5 research program and the translational oncology programs
6 at Stanford. My interest is actually designing first
7 in human trial of novel therapeutics, trying to
8 incorporate biomarker and patient selection in to see
9 how we can inform and expedite drug development. And
10 similar to David, I'm also interested because patients,
11 more and more patients are coming to us with molecular
12 profiling and how to assign them to clinical trials.

13 DR. LEMERY: Steven Lemery. As, as Joohee
14 mentioned earlier, I was involved in the, in the review
15 team for the pembrolizumab application. I'm a medical
16 oncologist, hematologist/oncologist by training and,
17 you know, have an interest in, you know, hopefully
18 helping patients at the end of the day.

19 DR. MOSCICKI: Hi. I'm Richard Moscicki. I'm
20 the executive vice president for Science and Regulatory
21 and Chief Medical Officer at PhRMA, the trade
22 association for pharmaceutical companies. I have a

1 very long history in my career of strong interest in
2 supporting the development of drugs for rare diseases,
3 and believe strongly in maintaining incentives for
4 innovation to continue the development for those
5 diseases.

6 DR. RUBIN: Hello. Eric Rubin. Medical
7 oncologist in clinical development at Merck. And I was
8 fortunate to be involved in the development of
9 pembrolizumab for the tissue agnostic MSI-high
10 indication.

11 MS. GAVIN: Good morning. I'm Pam Gavin here
12 representing NORD, the National Organization for Rare
13 Disorders. NORD is a nonprofit umbrella organization
14 that established itself 35 years ago actually this past
15 week, and through a grass roots advocacy effort to
16 really establish the incentives that we now discuss
17 and, and will be talking about as the Orphan Drug Act.

18 So, we are here today to ensure that the rare
19 disease patient voices are part of the discussions and
20 that the incentives that were established and refined
21 over time remain strong for the future.

22 DR. SUL: Okay. So before I ask Deb to

1 introduce the first topic, just two reminders. Even
2 though we're here at the, the great room at FDA, this
3 is not an advisory committee discussion. And secondly,
4 you know, I think any time you get into discussions
5 about tissue agnostic drug development, you know, sort
6 of the, the natural inclination is to go towards actual
7 talking about the clinical aspects. But this is really
8 a discussion to focus on the orphan regulation issues
9 that are, that are at hand. So just those two
10 disclaimers before starting.

11 DR. LEWIS: Could I, could I also introduce
12 Dr. Donna Roscoe. She'll be available for us as
13 any questions come up on testing elements. So, thank
14 you for being with us. I know -- were there any
15 clarifying questions? I know I received one during the
16 break. Did anybody have any others?

17 There, the question I was asked, are we the
18 same or different than in the European framework where
19 we may have limitations on how many designations you
20 can have and what type of criteria exists for
21 designation, multiple designations? And the answer is
22 that we actually, until approval, we'll continue to

1 allow designations for the same drug for that disease.

2 So, that is a little different than our European and our

3 Australian colleagues. You want me to go ahead with

4 this first? We're going to take --

5 DR. SUL: Oh, yeah.

6 DR. LEWIS: Oh, did you?

7 DR. SUL: Anybody else with any questions

8 specifically related to orphan drug designation or

9 exclusivity? I think one of the, the questions that

10 did come up earlier during the break was related to

11 drug. There were a couple slides, Debra, that you had

12 where you said, you know, if you have the same drug but

13 a different sponsor, you know, I think most of us are

14 used to thinking about drugs as sort of the name brand

15 drug. And maybe you could clarify a little bit about

16 what's meant by drug in the orphan drug regulations.

17 DR. LEWIS: Yeah. The regulations do set up

18 things differently for small molecules versus large.

19 And so I think Dr. Startzman can give us a little bit

20 about that.

21 DR. STARTZMAN: Yes, when we're talking about

22 same drug, in small molecule you're talking about the active moiety

1 and, you know, salts, esters, etc, do not
2 make them different. We do look at things like, you
3 know, differences in covalent bonds, etc. Large
4 molecules, you're talking about, you know, for
5 proteins, if they're minor changes, amino acid sequence
6 that can make a, that would make two proteins the same.
7 You know, they have to be major changes. And again, in
8 a lot of these things we do talk with the Review
9 Division in terms of what makes something the same or
10 different.

11 DR. LEWIS: So with that, I think that what we
12 tried to do in our preparations, we had some topics
13 that we knew would be important to answer. We'll,
14 we'll try to rotate between those if other comments
15 come up or questions come up. We welcome that. But I
16 want to go to first, Topic One.

17 PANEL DISCUSSION WITH AUDIENCE Q&A

18 TOPIC ONE

19 And this was a question just about -- this
20 goes kind of to the earlier discussions. What kind of
21 evidence would be necessary for FDA to consider a
22 biomarker as defining a tissue agnostic disease for

1 purposes of orphan drug designation? And again, the,
2 the real key for us is we have to keep in mind that
3 these sponsors often request drug designation very
4 early in development. But if there's any comments to
5 help us in -- now these, just as you said, this is not
6 an advisory committee, but we do appreciate this
7 feedback and that's the purpose of our meeting, to get
8 broad public input so we can consider this going
9 forward.

10 DR. KUMMAR: So I think -- I mean I'll get this
11 started. I think if you're doing it early on in
12 development, then there needs to be enough evidence
13 preclinically that first a biomarker exists across
14 certain, different histologies. We can debate the
15 number of histologies that it needs to be shown in, but
16 that the biomarker is present and then the modulation
17 of that biomarker has an effect in preclinical models.

18 I think that should be at least a minimum to
19 sort of consider whether you're going to do tissue
20 agnostic versus just one histology.

21 DR. LEWIS: Thanks. Other comments?

22 DR. MOSCICKI: Well, in considering this, you

1 know, I'm not sure that this panel will have the final
2 say on --

3 DR. LEWIS: No.

4 DR. MOSCICKI: -- what should define this and
5 so we think that continued discussions with
6 stakeholders should be necessary in order to really
7 come to any more definitive approach to, to what should
8 define a tissue agnostic disease with that biomarker.

9 However, you know, I do think that it's
10 important to maintain an attitude of flexibility as we
11 move forward towards that, in order to not dissuade
12 others from pursuing this approach, which is so
13 promising.

14 You know, I think at the same time it would be
15 useful in that discussion to come up with some idea for
16 sponsors as to what kind of data would be necessary
17 from biomarker negative populations as well, in order to
18 help them decide whether this is something they want to
19 pursue or not. So more about principles perhaps here
20 than actually scientific designation.

21 DR. LEMERY: Just to follow on, you might want
22 to comment, comment on this, though, is, is that it

1 sort of can go both ways, is that when you combine
2 everybody together, that's when you sort of, you know,
3 perhaps could go over 200,000, is sort of the cutoff.
4 So, you know, if we start thinking of early on is, is,
5 you know, are we granting a tissue agnostic indication
6 and it starts having indications above that 200,000,
7 then are you potentially limiting sort of disease
8 specific where, you know, you have to debate whether
9 it's appropriate to give an orphan designation in a, in
10 a biomarker of single disease setting.

11 So I, it kind of goes both ways, is whether we
12 have to really think about, you know, what is, the
13 flexibility and are you really fostering this or not
14 fostering it, and it may depend on that cutoff for that
15 indication.

16 DR. MOSCICKI: Well, that's why I think,
17 again, making sure that we have the appropriate
18 stakeholders who are focused on these issues at the
19 table when we try to come to those definitions. But I,
20 I think if we get too rigid in those definitions, we
21 may -- the science is so fluid here that, you know, I
22 think rigidity might restrict our ability to actually

1 make the decisions. And that's why I think flexibility
2 should continue to be considered as we try to nail this
3 down.

4 MR. KARST: I think it's worth -- sorry. I
5 think it's worth mentioning, of course, hey, this is an
6 evolutionary process. So, you might start out tissue
7 specific and you can go in for multiple orphan
8 designations. And as time goes on, as it, you gain
9 greater understanding, you can go in for a separate
10 tissue agnostic designation. The main benefit here,
11 designation really is the tax credit.

12 So, if you're doing -- if you get the
13 designation in a tissue specific disease, you'll do the
14 studies. You'll get the, the tax benefit. And again,
15 as time goes on, it may become apparent that it's a
16 tissue agnostic therapy and you could simply request
17 that designation prior to submitting a marketing
18 application and you'll still get the exclusivity in the
19 end provided you get the approval.

20 DR. LEWIS: So you've talked about flexibility
21 and being able to start with tissue specific, and then
22 with time as more information comes along there would

1 be a point where there's some agreement. What we've
2 generally done is align ourselves with the Review
3 Division input on how they're viewing things. But
4 others outside have suggested, no, we should be more
5 aggressive and start combining things based on targets
6 sooner. Do people see merit in doing that or is there
7 an issue?

8 DR. HONG: If you're, if you're asking should
9 you give designations just based upon like a
10 preclinical package versus actual clinical human data?

11 DR. LEWIS: I think where I'm focusing, we, we
12 have specifics on what we would request, but when would
13 we consider grouping? And I think Steve talked a
14 little bit about this. When do you group and when do
15 you split? We are hearing suggestions starting with
16 splitting and then at some point we'll become flexible
17 and we would group.

18 But is that something that, that should be
19 aligned with the, across our Agency with the Review
20 Division, or is this something that you envision
21 designation happening before an approval, before
22 there's been a tissue agnostic approval? Should we

1 start grouping?

2 DR. MOSCICKI: Once again, I think it's really
3 important that sponsors receive the appropriate
4 incentives and orphan drug designation provides such an
5 important incentive. I would hate to see -- I think
6 the sponsors should have the ability to choose the
7 direction that they want to go. And they may choose to
8 start with a tissue agnostic if that is the best way to
9 get a drug to patients, to the broadest group of
10 patients, rather than necessarily splitting it at the
11 beginning. So, I really think choice should be
12 important in, in how this is approached.

13 DR. HONG: I'm, I'm in favor of flexibility,
14 but I do think that we, as Shivaani already listed, I
15 think you have to have some basis for scientific, you
16 know, rationale. I mean like I think the pembrolizumab
17 is, is a good model. I mean there was clear hypothesis
18 that Dr. Le and Dr. Luis Diaz had shown in
19 their trials.

20 And, and more importantly beyond just the
21 preclinical, you know, just kind of understanding of
22 this, they actually started putting patients on in

1 their IIT studies who were not just colorectal and they
2 saw responses across histologies. So I think, in my
3 opinion I think you, you have to have, yes, that
4 preclinical package that, that hypothesis that makes
5 sense across histologies, but I think that in early
6 studies you have to show evidence that hypothesis may
7 actually play out.

8 And I don't, you know, I don't think it's --
9 at this point given the fact that oftentimes
10 preclinical data doesn't pan out in, in early studies
11 in humans, that you can just say, okay, here's my
12 preclinical package. I think this is across
13 histologies. I would like a designation. I think you
14 have to have some human evidence that hypothesis is
15 going to pan out.

16 DR. MELLIS: Yes. If, if I may interject at
17 this point --

18 DR. LEWIS: And if I can ask to pull --

19 DR. MELLIS: You're going to do that?

20 DR. LEWIS: Yeah. Pull that microphone close.
21 I'm, I'm getting word that if, if we turn up our mics,
22 the people online create, it gets feedback for them.

1 So that's perfect. Thank you.

2 DR. MELLIS: Okay. So my thoughts on this. I
3 agree with the comments about the importance of
4 flexibility and getting important medicines to as many
5 patients rapidly as possible. With respect to the
6 evidence necessary for designation, my, my feeling
7 about this was that clearly the evidence of rarity is
8 important and that a concept of plausibility and a
9 measure of evidence and a measure of consistency in
10 that evidence for designation is useful.

11 And currently the criteria for orphan
12 designation evidence indicates, if I understand
13 correctly, that it could be either clinical or in vivo,
14 or in vitro evidence. If it's strong enough that could
15 support designation. Naturally approval is going to be
16 dependent on the quality clinical evidence.

17 So I think if there's a hypothesis with strong
18 face validity and a measure of, say, possibly even
19 preclinical scientific information, that might be
20 sufficient for designation. I think one of the
21 interesting questions nested in here is with respect to
22 tissue agnostic indication. How many different tissue

1 types would need to be sampled or examined when you're
2 making a designation decision?

3 And the, the concept that Dr. Hong proposed
4 earlier about lineage, might you want to have evidence
5 from a number of tumors of different embryonic lineage?
6 That might be helpful. But I think that ultimately at
7 the end of the day, flexibility and the, the
8 plausibility and the potential to, to help patients
9 should be the overarching principles.

10 DR. HONG: I guess I'm all about helping
11 patients because I see them every day. But, I can't
12 tell you how many times I've seen preclinical factors,
13 they tell us this is going to be the most incredible
14 drug on the planet, and then we get into clinic and it
15 doesn't work.

16 And so I think that we have to be mindful of
17 that, that right now our in vivo and preclinical models
18 oftentimes do not translate into human beings.

19 DR. MELLIS: Yeah. That's definitely true,
20 but if we're talking about orphan drug designation,
21 we're not talking about an approval. There's, there's
22 a significant potential gap between getting designated

1 for, as an orphan drug, and the, and accumulating the
2 adequate evidence to actually achieve an approval.
3 And, and if you don't get there with human data, you
4 don't get there. You don't get approval and you don't
5 get exclusivity.

6 So, I'm, I'm not comfortable, I don't know
7 many other situations and maybe our, those of our FDA
8 colleagues here who are in the Orphan Drug office can
9 tell us whether you hold other orphan drug designations
10 to the necessity of having human data before you,
11 before you would grant the designation.

12 DR. STARTZMAN: Yes, for orphan drug
13 designation, I mean the, we, we love human data, but
14 usually we don't have it and we will accept animal
15 data, using the product in an animal, an appropriate
16 animal model for the disease. And only if animal data
17 or if an animal, if an animal model does not exist,
18 then we will look to in vitro data.

19 And we have had people come in requesting
20 designation for what looks like a tissue agnostic
21 disease or condition, and usually we go, if it's not
22 like MSI-high or, or NTRK, we go to the review division

1 and we say is there information available that this
2 marker could work across different histologies at the
3 present time.

4 And if they say at the present time we don't
5 have that data, then we have gone back and said, you
6 know, that we would not consider them for, for orphan
7 drug designation at this time. They can still get, the
8 disease then still becomes the, the histology or tumor
9 based, I mean organ based.

10 DR. MOSCICKI: But you're specifically
11 referring to tissue agnostic?

12 DR. STARTZMAN: Yes.

13 DR. MOSCICKI: Okay. Yeah.

14 DR. HONG: My last comment is I'm not asking
15 for randomized clinical trial data. I'm just asking
16 for a couple of patients across histologies showing
17 that, you know what, that may actually work across
18 histologies.

19 DR. LEWIS: More?

20 DR. MOSCICKI: I, I hear you, but I just don't
21 know that we should be asking for, you know, something
22 that we don't ask other situations for. And, you know

1 while we're very focused on oncology today, and
2 appropriately so, it's inevitable that what's decided
3 here will have precedent in other disease areas. I
4 mean as we learn more about autoimmune disorders and
5 some of the molecular basis that might trigger certain
6 autoimmune disorders, we may find that there are also
7 tissue agnostic opportunities that are molecularly
8 targeted in things like autoimmune disease where these
9 principles established here might very well spill into
10 there.

11 DR. KUMMAR: Yeah. I think I'm going to hear
12 what David's saying because I'm also a clinician, but I
13 think not to dissuade sponsors from going down this
14 route of a tissue agnostic, I think requiring some
15 preclinical evidence. But I mean if there is clinical,
16 that's great. I mean obviously you were made more
17 confident, but then sort of, because the sponsor's
18 also making a commitment, right?

19 Going tissue agnostic is not that easy, trying
20 to accrue across histologies and stuff. So, I think
21 having that flexibility and then requiring just
22 preclinical with any additional data that they may have

1 generated, or just the field has, as a scientific
2 rationale for the biomarker should probably be the
3 basis.

4 DR. SUL: I think the other issue to consider
5 is timing, you know, because a lot of these designation
6 requests come in early. And again, it's, you know, if
7 you go back to what the Orphan Drug Act was intended to
8 do, is to help with the development. So, I think that's
9 one of the reasons why people come in early.

10 I'm sort of, you know, playing devil's
11 advocate here because I think I also agree that
12 clinical data would be most helpful in making these
13 determinations. But, you know, again you have to sort
14 of think of what the, what the Act was intended to do,
15 is to encourage the development. And you may not
16 actually be there yet.

17 PANEL DISCUSSION WITH AUDIENCE Q&A

18 TOPIC TWO

19 DR. LEWIS: Thank you. Everyone on our first
20 topic. I think it'll kind of continue in a little bit
21 as we look at perhaps a scenario. Let me see if I can
22 go. Maybe I can't. I see. All right.

1 Our second topic, we, we tried to actually go
2 into scenarios. And so for the next topic we're going
3 to call 2, we're discussing the different orphan drug
4 designation scenarios. Once the, once Drug A, we're
5 going to call it Drug A, is considered as defining a
6 tissue agnostic disease. So, we've talked about what
7 criteria we might want. I'm asking you now to assume
8 we have considered it to be tissue agnostic for Drug A.
9 And this large blue box here is to indicate that
10 disease, that biomarker-positive solid tumors, that
11 we're now accepting as tissue agnostic.

12 So, I'll give a couple different scenarios.
13 One, the first one, is when the same drug, this is Drug
14 A, used for, could it receive orphan drug designation
15 just for histology specific disease? And they're not
16 coming in acknowledging that biomarker. They're not
17 saying I want to develop this as a tissue agnostic.
18 They're saying I want to develop it for, for example,
19 pancreatic cancer. Pancreatic cancer under 200,000.

20 Now this big blue box here, we're going to say
21 is over 200,000. Can you come in and take these bites
22 of individual diseases that overlap into the tissue

1 agnostic? Or is that a problem? Does that make sense
2 to folks? Drug A approved for biomarker X. It's, it's
3 not -- I mean it's been designated. I'm sorry. It's
4 been designated or considered to be tissue agnostic.
5 Let me know now what your thoughts are.

6 Can a sponsor come in, and for the same
7 marker, just be going for the individual disease?

8
9 DR. MOSCICKI: Yeah. I think the, when I
10 looked at this coming into here, I thought you were
11 talking about this is histology-specific pancreatic
12 carcinoma irrespective of, not defined by the marker,
13 right? So that's the scenario.

14 DR. LEWIS: Mm-hm, has overlap. That's sort
15 of we're trying to draw -- there are members of that,
16 of that pancreatic cancer that share that marker.

17 DR. MOSCICKI: Yeah, so as, as we've thought
18 about these things, we would establish first several
19 principles to think about each of these moving forward.
20 And, and, you know, I think we represent one viewpoint.
21 I recognize there might be others, but, but we believe
22 that the Orphan Drug Act has been enormously successful

1 and continues to be an important pathway to provide the
2 right incentives for innovation and rare diseases.

3 And so we should continue to try to keep and
4 encourage policies that maintain these robust
5 incentives for sponsors to do the investments necessary
6 to study drugs to move forward in, in rare diseases,
7 and to do it as robustly as possible once again.

8 So, and then as we thought about the various
9 convoluted scenarios that can occur when you start
10 overlapping and splitting and so on, we think that a
11 policy that would be simple and most straightforward
12 to, to address most of these is to really consider
13 biomarker-targeted tissue agnostic indications as
14 different from histologically defined disease.

15 DR. LEWIS: Complete, completely different.

16 DR. MOSCICKI: Yes, that they are different.
17 They are differently defined. They're not -- and here
18 I know we get into this what is a disease, and what is a
19 condition, and what is an indication?

20 But we, we feel that if we by policy, whether
21 in practice it's true or not, but by policy if we would
22 propose that these are, in fact, different and should

1 be treated as different, we will avoid a lot of the
2 convolution discussions that various different
3 scenarios will inevitably present themselves with.

4 So, I didn't intend to go first here, but with
5 those principles, you know, we would say, yes, on the
6 scenario based on that.

7 DR. STEWART: Sure. I have a few thoughts
8 maybe from a different direction. It brings up a point
9 that was raised earlier in terms of like the kind of
10 structure, the clinical trial that led to Drug A
11 getting the approval in the first place for a
12 biomarker-positive tissue agnostic disease and whether
13 pancreatic cancer was originally a part of that and how
14 much information we might want to know on the biomarker
15 negative disease, and whether that information could
16 have been teased out in the original trial that led to
17 Drug A getting the subsequent approval for a histology
18 specific disease that's independent of that biomarker.

19 You know, and I recognize, and I think
20 everyone in the room recognizes the importance, and the
21 fact that information evolves over time, and I look at
22 that red circle and I think of a patient. So anything

1 that's outside of that blue line with this new approval
2 is more patients having access to a drug that they may
3 not have had access to before.

4 So, you know, I look at it as if this
5 information weren't on the label, how does that affect
6 patients and their access to this therapy, and does it
7 benefit patients having this additional information on
8 the label. I mean it ties back to some of our work in
9 terms of ensuring that FDA labels are up to date and
10 have accurate information.

11 And if, you know, that information isn't
12 critical to ensuring patients have access to therapies,
13 and, you know, it think it's important. But clearly it
14 just depends because you don't know the time from the
15 Drug A's original approval from the second, and whether
16 it required maybe a new clinical trial, and whether it
17 still meets the spirit of the orphan drug designation.
18 In my opinion, in terms of ensuring patients with rare
19 diseases have access to therapies that they wouldn't
20 otherwise have access to.

21 MR. KARST: So Dr. Lewis, I think it comes
22 back to how one your, your slides in your presentation.

1 You designate drugs, biologics for diseases or
2 conditions and they're approved for indications. So it
3 really comes down to what you identify, how you
4 identify the disease or condition. And, and it, so the
5 slide almost answers the question, right? Where we
6 have a biomarker positive tissue agnostic disease that
7 is the disease or condition, can it then, Drug A
8 receive designation for a histology-specific disease,
9 which is a different disease?

10 So insofar as we're talking about different
11 diseases or conditions, I would certainly think that,
12 that a paradigm here where you could get designation
13 for the histology-specific disease makes sense because
14 you're defining the disease or condition as histology
15 specific.

16 DR. MOSCICKI: Plus it certainly doesn't rule
17 out the possibility that the pancreatic cancer
18 indication or disease specification is different
19 because it could be that despite the agent being
20 effective in biomarker X positive solid tumors,
21 pancreatic carcinoma might be a unique circumstance
22 where it works even in those that are negative for

1 biomarker X.

2 And so, you know, I think to preclude giving
3 an orphan drug designation to pancreatic carcinoma here
4 would not be appropriate. And might cause, again, a
5 dissuasion, if you will, of a sponsor to, to continue
6 to pursue the specific studies that might have led them
7 to think that pancreatic carcinoma was an area that
8 they should pursue.

9 DR. LEWIS: Oh.

10 DR. MOSCICKI: Nor should I think we -- nor do
11 I think we should add burden to the sponsor by
12 requiring them now if they believe that pancreatic
13 carcinoma, and they have evidence that pancreatic
14 carcinoma might respond, to try and separate and
15 subdivide pancreatic carcinoma based on the biomarker
16 itself if that's not what they choose to do.

17 DR. HONG: I would argue it, it depends. And
18 if you were to change that out for colorectal cancer,
19 right, and MSS-high, let's say it was less than
20 200,000, which is not true, but let's say it is.

21 DR. LEWIS: All right.

22 DR. HONG: And you have this data from

1 biomarker positive studies on the keynote studies that
2 show that zero patients responded to, who were MSS
3 stable, and then a drug company came and said we want
4 to do, try to get, an orphan drug designation in
5 colorectal cancer irrespective of MSI-high status. I
6 would say, if I was an FDA officer, I would say no.
7 Look, look at the biomarker study. Zero out of
8 whatever X patients showed no response in the biomarker
9 positive, you know, pivotal studies. Please do not
10 submit an application. Remember I, I'm all about --
11 trust me, I'm all about getting drugs to patients. I,
12 I see them every day and I see many of them dying.

13 But I'm also about do no harm. These drugs do
14 not, are not benign drugs. They cause, can cause
15 severe side effects. So, I think it all depends. It
16 depends on what that biomarker data shows. It depends
17 on -- obviously this is designation. This is not
18 approval. I understand that. But it all depends.

19 DR. MOSCICKI: That's an important point.

20 DR. SUL: Are you, are you talking about -- so
21 then are you talking about whether or not for, for an
22 actual traditionally defined disease, whether or not

1 any responses or activity that you're seeing is
2 actually being driven by the biomarker population and
3 sort of teasing that out, being able to, to identify
4 that --

5 DR. HONG: Yeah, if that's available.

6 DR. SUL: If, if the data is available.

7 DR. HONG: Yeah.

8 DR. KUMMAR: In reality the sponsor wouldn't
9 go for a biomarker negative unless they have some
10 rationale to say that the agent would have activity in
11 that population. And I think we need to do everything
12 to encourage sponsors to look at biomarker negative
13 also because, you know, we don't know depending on the
14 biomarker that we're dealing with that maybe its
15 activity is driven by an off target or a second target
16 effect off a small molecule that's being testing.

17 But in this particular scenario, the
18 difficulty I was having when I was reviewing this is
19 that if, it's still Drug A and if I'm Sponsor A, and
20 it's my drug and I already have a designation for your
21 biomarker positive cohort, that already includes
22 pancreas that is biomarker positive.

1 So then why wouldn't I just apply to get
2 orphan drug designation for biomarker negative
3 pancreatic cancer and just get the orphan drug for
4 that? Then I'll have for both, right? Or did I just
5 miss this?

6 DR. LEWIS: No. I think, I think your point
7 is good and it might be a good time then to look at our
8 next scenario. I think we've heard a little bit from
9 each side and why it's helpful for us to hear these
10 discussions is because people have suggested, oh, maybe
11 you should not be designating all of these. Maybe
12 that's a misuse, and as soon as a target is shared you
13 should start to designate as soon as there's a shared
14 target.

15 And that suggestion has come to the Agency and
16 people have disagreed. We will see as we go along,
17 will we just be staying in the same place where now we
18 continue to designate all histology specific if we look
19 at them as totally different diseases.

20 But let me just move to run next - yeah, I
21 can, I have to get to right here. You just mentioned
22 target negative. And so another way of, of approaching

1 some of these questions as we're still talking about
2 the same situation where Drug A was recognized as a
3 tissue agnostic situation for this big blue disease
4 here. And now we have someone requesting specifically
5 marker negative pancreatic cancer. And this might be
6 an easier topic to, to reach agreement on.

7 DR. MELLIS: Yeah. From, from my perspective,
8 why not? I mean if, if one develops the evidence that
9 in this rare subset of a rare cancer that the drug is
10 likely to be efficacious, then it, the incentives
11 provided by the Orphan Drug Act are important to enable
12 the sponsor to invest, to test that medicine, and see
13 whether it can be brought to more patients living with
14 rare disease.

15 DR. KUMMAR: Yeah, I think this is exactly
16 what I would think would really help because we do want
17 to encourage, not sort of close it off saying it's just
18 going to be active in a biomarker positive population.
19 So this would encourage people to look at specific
20 subsets. And if it made some of the common diseases
21 rare if you start doing this kind of division of a
22 biomarker negative, so, which would be a good thing

1 because we want to evaluate across histologies and do
2 this kind of categories.

3 DR. RUBIN: I would agree and I guess that,
4 you know, one question that was back to what, what
5 level of evidence would you need for the potential for
6 activity in the, the negative population.

7 DR. LEWIS: Well, one of the things that was
8 said earlier by Dr. Startzman when he talked about the
9 actual evidence we, we prefer human data, we oftentimes
10 need to look to appropriate animal models in general in
11 designation. But it's really the same, the same
12 situation. Someone said, well, we shouldn't, we
13 shouldn't hold tissue agnostic to a different place.

14 If we have a question about whether, whether
15 we have a proper designation situation, we have a great
16 consult process that we can work across our Agency to
17 be able to do that. So we have some of the tools
18 available to us to help answer these questions.

19 And so I know we're not, are not seeking
20 agreement, but we really do want to hear people's
21 different opinions. But that is one thing I can say,
22 is that we're fortunate to have terrific colleagues

1 across the Agency to help answer any questions we have
2 about whether it's disease or otherwise.

3 And I know we -- do people think we do have
4 adequate tools and, to be able to address the, these
5 questions that we're asking?

6 DR. HONG: I do -- I think yes and no. I mean
7 one, one question is, I had in the context of
8 biomarkers is, you know, we have this cutoff of 200,000
9 patients. And I, and I'm just thinking about my own
10 experience with NTRK. Like we don't really know what
11 the prevalence is in the, in metastatic cancer. I mean
12 we, we assume it's less than 200,000 just because, you
13 know, we've, we've screened patients and we've, you
14 know, there have been larger datasets like from Charis and
15 so forth that have looked at it.

16 But, but the reality of it is that we don't
17 really know because, you know, TCGA and even CABIO, they
18 don't really, they don't really test the, the
19 population that is really, these indications are for,
20 right? So, so that's one question that, you know, is,
21 is up in the air because I, you know, people always ask
22 me, well, how many NTRK fusion patients are out there?

1 I said I, to be very frank with you, I don't really
2 know yet. There could be a lot.

3 DR. LEWIS: And, and one, one of the fine
4 points that we didn't talk about earlier is we have to
5 make our determination for designation based on the
6 science that is present at the time of the application.
7 And so once in a while we're in a situation where
8 something could be designated and then later on, as you
9 talk about, there might be additional testing
10 information that would change that number.

11 We would not remove the designation because at
12 the time of designation request we will honor that
13 prevalence that's anticipated. But it's at that time.
14 But as new information comes along, we will use that
15 information at that time. Is there anything, other
16 regulatory-wise? I know people might have thoughts
17 about just --

18 DR. MOSCICKI: Well, this seemed the most
19 clear-cut of all the scenarios.

20 DR. LEWIS: Yes, I thought it was a good one
21 too.

22 DR. MOSCICKI: Since there's no, no overlap

1 theoretically or otherwise in, in the disease or
2 indication. I guess I would ask a question, though.
3 You know, when Drug A -- I, I know you can't give a
4 designation for the same drug for the same indication.
5 Clearly not the situation here. But when you have even
6 in, say, this sort of overlapping situation, just
7 because you have an orphan drug designation doesn't
8 mean you actually will turn out to be successful.

9 And so, again, I think it's important not to
10 de-incentivize the willingness to pursue another area
11 where it might turn out to be actually effective when
12 the tissue agnostic doesn't end up bearing out. You
13 know, so that's a difference between having already an
14 established market approval versus just having a
15 designation. And something that we should keep in mind
16 as we think about it.

17 One of the issues that we thought about when
18 we sort of said, you know, the simplest way here to cut
19 this Gordian knot is to just say --

20 DR. LEWIS: Move up.

21 DR. MOSCICKI: Okay. I usually don't have
22 trouble being heard.

1 DR. LEWIS: You're, I, what, what, my
2 understanding is we're, we're heard in the room, but
3 the electronics are, are not as good as hearing is for
4 the webcast people. Mm-hm.

5 DR. GAVIN: Debra, to answer your question, we
6 would say that you do have the appropriate paradigm in
7 place to, or the tools in place to address this if you
8 look at these sub, sub-orphan, the sub-common disease
9 paradigm, you could use here quite effectively the
10 draft guidance as an example to reference.

11 DR. LEWIS: Thank you.

12 MR. KARST: I'm curious how the scenario,
13 curious how the scenario really differs from the first
14 one. I mean maybe Dr. Startzman or Dr. Lewis can
15 answer. And if somebody went in here for designation,
16 would they not receive designation for pancreatic
17 cancer, right? Just as in the first example. And then
18 they'd simply get that designation and ultimately get
19 approval for the, you know, biomarker X negative
20 pancreatic cancer patient.

21 So it's kind of that, getting that piece of
22 the pie approved. Is it, is it really any different

1 than the first scenario where you're getting
2 designation for a specific disease or condition here,
3 whether it's pancreatic cancer or the tissue agnostic
4 biomarker?

5 DR. SUL: So actually I'm, I'm really glad you
6 asked that question because it seems like, you know,
7 the consensus up here is that, that there really is no
8 problem with identifying this biomarker X negative
9 histological disease as a separate entity. And, and I
10 -- and maybe I'm just not getting it, but in my mind,
11 you know, there's a huge difference in defining
12 something by the absence of a biomarker versus the
13 presence of one.

14 I mean if you think about something like non-
15 small cell lung cancer where you can slice that pie
16 into, you know, multiple different biomarker positive
17 populations, does that mean that everyone who's ALK
18 negative is the same cancer? I mean I, I guess I'm
19 still behind then in not quite seeing this as, as
20 definitively as a separate disease.

21 And part of it is, I think, also that, you
22 know, it, it really goes back to that crucial question,

1 the slide that, that Dr. Lemery put up, is, you know,
2 what is the disease versus an indication? And I think,
3 you know, part of the issue is that that Orphan Drug
4 Act was really, you know, conceived at a time before
5 the science came out. It just may not be -- some of
6 the way that it's written may not be a great fit for
7 how we're thinking about things now.

8 You know, in my mind a disease is something
9 that, that effects a body or a person. You're not
10 going to go see a doctor for, you know, a specialist in
11 NTRK-positive tumors. You go see a breast cancer
12 doctor or a colon cancer doctor. You don't go to see
13 an ALK-positive oncologist. So, in my mind the disease
14 is still, you know, what affects the, the person.

15 DR. LEWIS: Perhaps, perhaps if this is
16 something that's really getting people hung up on about
17 the disease, you may want to think about is it proper
18 to incentivize and provide -- is that the good use of
19 the Orphan Drug Act to, when we recognize that we could
20 be able to generalize across? Now this is not this
21 scenario, but just in general to address this question.
22 If we can generalize across the disease, is it

1 reasonable that we divide it into all of its member
2 pieces? Or should we be incentivizing it as a group
3 once we know?

4 DR. MOSCICKI: The more incentives the better.

5 MR. KARST: One thing I'll comment, comment on is that I
6 think

7 you've shown it here as the, the red circles

8 overlapping with the square --

9 UNIDENTIFIED MALE SPEAKER: Sorry to
10 interrupt. Could everyone bring the microphone a
11 little closer, especially when you're speaking side to
12 side?

13 MR. KARST: But it could be different if,
14 obviously you could have different circles if that red
15 circle was outside the square or inside the square.
16 Not to have more complexity, but that, that is, could
17 be part of it.

18 DR. LEWIS: Yes, yes.

19 DR. MOSCICKI: And, and recognizing that maybe
20 the science is only at a certain point in how you
21 define biomarker negative or positive. But you already
22 established that you have to work with what you know at
the time that you know it. And, you know, so I, I

1 think that you still have to assume that you can
2 differentiate these. Otherwise, why consider the
3 biomarker positive population, I would even argue.

4 So I think the other part here still comes
5 back to this idea that, yes, it's positive that,
6 possible that for biomarker positive solid tumors in
7 this scenario you might have an 80% response rate. But
8 let's say in biomarker negative pancreatic, there's
9 something about pancreatic. Maybe it's how it
10 expresses the biomarker on its surface, but still has a
11 similar basis for a mechanism of action of the drug
12 that you now get a 40% response. Maybe it's not the
13 same, but it's still certainly worthwhile and certainly
14 an orphan drug designation, right?

15 DR. STARTZMAN: And just, you know, from my
16 perspective if I would see this scenario, I would be
17 having a tendency to say, you know, my, my question
18 would be why aren't we expanding it to pancreatic
19 cancer instead of designating it just for biomarker X
20 negative? I mean that's really the question.

21 MR. KARST: I guess the only reason you would
22 is if pancreatic cancer were, let's say, over 200,000,

1 and you had specific data showing that, you know,
2 biomarker X negative and your product worked only in
3 that population, then it would be designatable as
4 an orphan. I mean, but I agree with you. I mean
5 broadest designation policy, possible, it's been your
6 policy for decades.

7 DR. STARTZMAN: Because that's why we picked
8 pancreatic cancer.

9 UNIDENTIFIED FEMALE SPEAKER: I want to go
10 back to the, the point someone made about whether the
11 red circle is outside or inside the square. And that's
12 a very relevant point because we're talking about very
13 early development. These biomarkers still haven't been
14 clinically validated and they haven't shown clinical
15 utility in some cases.

16 And it does have a huge, huge impact on how
17 you accrue patients, because we're talking about very
18 early studies where sometimes you have preclinical
19 proof of biomarker efficacy, but you don't have an
20 assay that's been developed and you're sometimes
21 accruing patients based on histology, not necessarily
22 on the biomarker profile which may come later on.

And I would really love to hear CDRH's

1 thoughts on this. But it does have an impact because
2 we're still talking about designation, not approval.
3 And as you're, you're accruing patients for the
4 studies, this does have an impact. So that was a point
5 I wanted to make.

6 DR. LEWIS: Sure.

7 DR. ROSCOE: Is this on? I think she kept
8 seeing me raise my hand because I was desperate to say
9 something. Because in this model you really do need to
10 understand and have a really good working definition of
11 the biomarker because what is negative is going to be
12 defined by however you're measuring that biomarker. If
13 you're looking at wild type, wild type is only defined
14 by the mutants that you're actually looking for.

15 Dr. Hong mentioned there's a threshold. You
16 could easily have a test that has a high threshold to
17 define biomarker positive, but the inverse of that is
18 not going to necessarily be biomarker negative. And
19 now you've designed a trial that efficacy may be coming
20 from the residual biomarker positives that you're
21 actually calling biomarker negatives.

22 So, this is significant, and what we saw with

1 MSI-high was what went forward was that a biomarker was
2 defined based on the standard of care testing and a lot
3 of knowledge was understood about that in terms of the
4 concordance between the IHC and the classic PCR for the
5 five loci, but what's come out of it now is a lot of
6 NGS testing with, you know, numerous denominators on
7 the panel and different thresholds.

8 And what you can see when you look at
9 abstracts of literature, very interesting information
10 going forward from like meetings like AACR and ASCO, is
11 that the prevalence with these NGS tests is different.
12 It varies from like 3 to 15%. So that's not in the
13 best interest of the patient. I've been at meetings
14 where I'm listening to people talk about false
15 negatives with IHC because their NGS test is
16 detecting it, but what is the evidence for that?

17 We don't have any response, which goes again
18 back to what Dr. Hong was saying, is give me a little
19 bit of something so I can work in the best interest of
20 the patients. Patients have to be really educated now
21 and ask what test am I actually getting tested with
22 because if they're really interested in being motivated

1 to get that therapeutic, they want a test that's going
2 to have a high prevalence on that biomarker.

3 UNIDENTIFIED FEMALE SPEAKER: And I'm going to
4 add one more point to that, which is we've been talking
5 about rare diseases, and one thing we also have to
6 think about if we're talking about the biomarker
7 interfaced with the histology and the disease is what
8 is a rare biomarker? We have data on prevalence of
9 disease. We don't often have data on prevalence of
10 biomarkers in that context of histology.

11 DR. SUL: So yeah. I think those are --
12 they're, they're definitively good points and, and
13 certainly, you know I think we, we consider these,
14 especially during the development process, and when
15 we're looking at these trials and how these trials are
16 designed.

17 But, you know, I think when the, the Office of
18 Orphan Products are, are getting these applications for
19 designation, these are often coming in way before, you
20 know, any tests are being developed and the clinical
21 trials are being designed.

22 And I think this is, again, you know, we're

1 sort of running into overlapping discussions where
2 there's the drug development side of things and the
3 clinical trial design side of things versus the
4 designation, which is really, again, I think, you know,
5 what Deb said earlier, sort of recognizing an entity
6 for potential incentives and, you know, what are the,
7 the thresholds for that.

8 DR. KUMMAR: But I think one thing -- I mean I
9 don't think any one of us is thinking that the biomarker
10 negative cohort is a homogeneous cohort of pancreatic
11 cancer, right? I mean all it is, based on what Eric
12 was referring to, is that you have a preclinical
13 package or some rationale to say that maybe this drug
14 will have activity in a biomarker negative pancreatic
15 cancer.

16 It may turn out to be because it's biomarker
17 Y. It may turn out to be that the biology of X is
18 different in this particular population. And so you'll
19 see a different response rate in this.

20 And so I think it's just incentivizing
21 sponsors to investigate this population and then if the
22 response is, people will go figure out why it's

1 working. But I think having some sort of designation
2 that kind of encourages people and not just go for the
3 low hanging fruit of just biomarker positive.

4 UNIDENTIFIED FEMALE SPEAKER: Can I ask a
5 question?

6 DR. LEWIS: Yes. We're, we're broadening our
7 format.

8 Dr. SUL: Can you please state where you're from, your
9 name and where you're from?

10 MS. SEARS: Yeah. My name is Abitati
11 (phonetic) Sears (ph). I work in the (inaudible). So
12 one of the criteria to get orphan designation
13 in a subset is that your, your drug is not
14 appropriate outside of the subset, right? So in this
15 case, or in the other case, if you get your orphan
16 indication of the blue square and then you come and you
17 show that your activity works in the biomarker
18 negative, pancreatic, would you lose orphan for the
19 blue? Because now you're showing that you actually
20 work outside a subset?

21 DR. LEWIS: Thanks for your question. I, I
22 think it is worth clarifying this. If you do -- in
this case we just said that we've considered this

1 target to be, to be a tissue agnostic target. But
2 let's assume that you're saying, yes, it has a
3 designation. The only thing that we're adding to that
4 is somebody else coming along, say, for this other
5 specific designation. You will not, it will not affect
6 the blue square's designation. It will stay in place.

7 The only time we generally have the authority
8 to remove a designation is if at the time of the
9 request the, there was evidence that it didn't, it
10 wasn't eligible at that time. There could have been an
11 omission of information that should have been there.
12 It could have been an error. But if at the time they
13 weren't eligible from omission or -- what else do we
14 have there?

15 Just generally have, it would be that you
16 weren't eligible at that time. Maybe the prevalence
17 was shown to be over that, but it was not identified.
18 That's very uncommon that we remove a designation. And
19 this would not be a scenario where a designation would
20 be at risk because at the time of the first one, the
21 information qualified for designation.

22 DR. STARTZMAN: Yes, and I think in this

1 we're not really talking about subsets. I mean we're
2 talking biomarker X solid tumors is a disease. It got
3 designated if, if that's the case. In this it doesn't
4 really necessarily, but let's say it was. Let's say it was
5 under 200,000 and it got designated for biomarker X
6 positive solid tumors. And then later they're coming
7 in and talking about pancreatic cancer more in the
8 histology defined disease. So we would say that's a
9 disease. So we're not talking about orphan subsets.

10 DR. LEWIS: So if they're both rare, both the
11 blue box and the, and the pancreatic were rare, that's
12 one set of circumstances. But I think sometimes when
13 people think about this question, they think if the
14 blue box represented a common condition, a grouping
15 that we believed was over the 200,000, then, one of
16 our panelists has said more incentives the better and
17 that, that is, that is a philosophy.

18 But some people will say, no, you need to
19 really ensure you're incentivizing in a way that
20 doesn't allow -- some people have said gaming of, of
21 the Orphan Drug Act. Or other such things. But we
22 look at it as we have protections, just as Pam Gavin

1 was saying. We have protections that allow us to
2 protect the Orphan Drug Act and we want to do that
3 responsibly.

4 And that's -- whether it is we should allow
5 the, this to be looked at as two different diseases is
6 a very important aspect, or whether we should really
7 consider the overlapping and, and subtract out that
8 overlapping aspect.

9 Those are, those are questions that are
10 important to us. Does that answer your question?
11 Okay.

12 DR. MOSCICKI: Yeah. The, the consideration
13 by some of, regarding that this is some kind of gaming,
14 again, I think is often misinformed. And I think it's
15 important to make sure that we clarify the fact that,
16 let's say this product gets approved for biomarker X
17 positive solid tumors and then three or four years
18 later comes along with the idea, you know, there's
19 evidence that this stuff really might work in, in
20 biomarker negative pancreatic carcinoma.

21 So it's important to recognize that when the
22 seven years is up for biomarker X positive solid

1 tumors, it's up for that. It, it doesn't extend that
2 exclusivity. It's only, related to the unique
3 indication that came along later because of additional
4 scientific work that was done by either, by someone to,
5 to recognize that that, in fact, was a, a good place to
6 use this drug.

7 DR. LEMERY: I guess I'll give you a scenario
8 that I'll become the CEO of the 28th different PD-1
9 inhibitor and I'm going to decide to investigate in --

10 DR. MOSCICKI: Get out of the business.

11 DR. LEMERY: -- tissue agnostic MSI setting
12 and yet I'm going to, I'm going to do my strategy where
13 I'm going to request an application first in MSI
14 positive, pick a tumor type that'll sort of, you know,
15 that, that cut will be under 200,000, but yet the whole
16 broader population will be above, you know, knowing
17 full well I could submit the application three days
18 later with a tissue agnostic, you know.

19 You know, those sort of scenarios could happen
20 where -- so I'm hoping to get the incentives, you
21 know, being the 28th one I'll have, you know,
22 exclusivity to prevent biosimilars in the market.

1 I think that, so there are potential, you
2 know, ways where companies could sort of creatively
3 think about opportunities to use the system that maybe
4 really aren't the intent of the, you know, really
5 fostering innovation.

6 You know, I suppose that's possible, but
7 again, I think the original intent is to incentivize
8 sponsors to conduct these studies. You know, if you,
9 if you said you were just carving out biomarker
10 positive solid tumors, you are carving out pancreatic
11 within that subset, then that would make sense, right?

12 But, but if you're actually getting new
13 information on biomarker negative pancreatic carcinoma,
14 you know, that to me is important. That's what we want
15 companies and sponsors to do. We want to get more data
16 to understand how to better treat our patients. So
17 that's why the Orphan Drug Act is there.

18 MR. KARST: From a generic drug perspective, I
19 definitely agree. I mean it's important to have very
20 black and white lines. Sorry, very black and white
21 lines on the indications and the scopes of the various
22 exclusivities for generic drug manufacturers because as

1 you have staged approval, staged periods of orphan
2 exclusivity, generics have to be able to carve out
3 those orphan protected indications.

4 So, if you have a bleed over on a graph like
5 this, it makes it very complicated to create a label
6 for generic drug manufacturers that omits that
7 protected population. So, I definitely agree with Mr.
8 Moscicki that it's good to have very defined periods to
9 certainly foster generic competition.

10 DR. LEWIS: Perhaps we can look at something a
11 little different. It looks very similar, but what
12 it's, we're again starting with the same blue box, but,
13 but what happens in this scenario is should FDA
14 consider orphan drug designation limited to histology
15 specific disease, but it's this, this drug has a
16 different active moiety.

17 So now it's a different drug, but it does have
18 the same or similar mechanism of action. In other words,
19 we expect it to be a histology -- I'm sorry, a tissue
20 agnostic type of drug. The sponsor only comes in,
21 though, with their histology-specific tumor
22 information. Again, we're using pancreatic cancer as

1 rare, but they're only submitting for the pancreatic
2 cancer, and yet we would expect this different drug to
3 be very similar in action.

4 DR. LEMERY: And that was sort of the example
5 I just gave about a PD-1 inhibitor for looking only at
6 endometrial cancer, neuroendocrine tumors, something
7 like that.

8 DR. HONG: I think it depends, again, and I'm
9 a big believer that, you know, we, I agree that the
10 orphan drug designation needs to be flexible and needs
11 to give incentives. At the same time we shouldn't be
12 harming our patients. And even those patients who are
13 eventually going to go on a clinical trial because of
14 this designation. And if we have data to say that this
15 drug has no clinical, you know, necessarily any more
16 benefit than an existing drug out there, I'm not
17 entirely sure, you know, you could give it a
18 designation, let alone --

19 DR. LEMERY: Let me --

20 DR. LEWIS: Yes.

21 DR. LEMERY: I think a, I think a better
22 example is not necessarily, people are thinking of PD-1

1 and that it doesn't work in pancreatic cancer. It may
2 be, I don't know the incidence, but like take, you
3 know, PD-1 positive gastric cancer, which has an
4 indication in pembrolizumab or, you know, something
5 with the response rate may not be 0%, but it may be,
6 you know, your indication in the biomarker positive is
7 a 40-60% response rate. But you might have an
8 unselected 5 or 10% or, you know, maybe even high --
9 you have a different response rate and there may be a
10 population in there where the drug works at, and
11 so there are, you know, clearly for melanoma and lung
12 cancer and some other indications,
13 you know, these drugs are working through an
14 independent pathway besides MSI. So whether it's PD-1,
15 whether it's, you know, TMB, all kinds of other
16 biomarkers are being studied, but, you know, perhaps
17 you can get a single disease where the company studies
18 in and, you know, proves that they do a randomized
19 study, for example, in, and gives predominance of
20 evidence that the mechanism of action is not driven
21 solely by MSI, that may be the situation here.

22 So pancreatic cancer is probably not the best example if
everyone has PD-1 inhibitors in their head.

1 But, you know, perhaps another, you know, cancer we're
2 not thinking about that really hasn't been studied very
3 extensively might be a better example.

4 DR. MOSCICKI: Yeah. Plus I'm a little
5 confused why there's even a question given that there's
6 a different active moiety. I think we've been very
7 clear about this in the past, right, that a different
8 active moiety is a different drug and has the same
9 ability to -- it's not the same drug. It is a
10 different drug even if it has a similar mechanism of
11 action.

12 And we know that there are plenty of examples
13 of similar mechanisms of action, but differences in
14 adverse events, differences in toleration, difference
15 in, you know, even effectiveness, or duration of
16 action based on the difference of the moiety despite
17 the mechanism of action. So, you know, I, this also
18 seemed pretty clear cut.

19 DR. LEWIS: There's -- do you want to explain
20 that subtlety of the, of the data?

21

22 DR. STARTZMAN: To me it was just, again, it's

1 whether you designate for -- early in discussions about
2 all of this we talked about -- when we were talking
3 about tissue agnostics, there was, there was talk that
4 if you target a specific, we'll just say, you know,
5 biomarker that is eligible for tissue agnostic, that
6 becomes the disease. And then all the sudden these
7 other smaller, you know, you know, like pancreatic
8 cancer, etc., would not be eligible.

9 I do think that like for instance you can say
10 that outside that biomarker driven tissue agnostic
11 disease you could see a benefit in, in, say, in
12 pancreatic cancer, etc. But that was what we were
13 really trying to, to determine in these. If it targets
14 a biomarker that's eligible for tissue agnostic can
15 they still get designation for a histology-specific
16 disease?

17 And in this case we were saying, well, say the
18 drug's different, but it still works through that
19 biomarker, can you get designated for the pancreatic
20 cancer?

21 DR. MOSCICKI: Yeah, but it's different.

22 DR. STARTZMAN: Well, but I mean let's -- in

1 the, in the same one, I think you had said you could
2 get designated for the pancreatic cancer. So yeah, so
3 it's different, I think.

4 DR. MOSCICKI: I mean I start there, but I
5 would still go back to the same principle that these
6 are different diseases. They're defined differently.
7 And so, so the answer would be yes there and yes there.

8 DR. LEWIS: I think the, the, as you were just
9 saying, Chip, there was, if, if you follow your approach that
10 everything's different, yes. It's always going to be
11 yes and yes. If you look at it from the perspective it
12 depends for those situations where you have the same
13 mechanism, but we don't have any data to, to talk about
14 the tissue agnostic mechanism. It's all about the
15 individual cancer.

16 Would we expect to have tissue agnostic
17 information? Would we require that because we have
18 already recognized that this mechanism has a tissue agnostic
19 attribute to it? So --

20 DR. MOSCICKI: Yeah, but the moiety is
21 different. I mean we have different ACE inhibitors --

22 DR. LEWIS: Yes, the --

1 DR. MOSCICKI: -- we have different -- you
2 know, they act -- the mechanism of action could be the
3 same, but we know they have different profiles. We
4 know responses differ and we should not, you know, deny
5 an incentive to a company that wants to bring an
6 alternative to the patients because it has a different
7 moiety despite a similar mechanism of action.

8 I thought the more interesting question here
9 might be, you know, could a different moiety then get
10 the same biomarker X positive solid tumors, right?

11 DR. LEWIS: Yes.

12 DR. MOSCICKI: And, and once you say that,
13 then why would you say no to even moving outside the
14 blue box? You know, so that's why I, you know, again,
15 this one didn't seem to be that complicated.

16 DR. LEWIS: So to interpret your, what you
17 just said, would the designation in your mind be either
18 of those? It would be either the tissue agnostic or
19 the histology specific?

20 DR. MOSCICKI: It could be as long it was
21 truly a different active moiety. The lawyers can tell
22 me different, but.

1 DR. MELLIS: Yes. Yeah, I would like to agree
2 that each drug that is different drug should be
3 evaluated on its own merits. And it does seem like our
4 state of knowledge is in rapid evolution and our state
5 of practice is in rapid evolution. But if indeed
6 there's, there's a literature out there that says that
7 biomarker positivity may have something to do with
8 efficacy in, in one or another cancers, particularly
9 this one, then, you know, maybe, maybe it ultimately
10 does behoove the sponsor to, to test in the positive
11 and the negative subsets prior to approval.

12 But fundamentally, I think each drug should be
13 evaluated on its own merits.

14 DR. KUMMAR: Just to extend that question. So
15 when the sponsor comes to you for the pancreatic cancer
16 designation, and you already know that this biomarker
17 may have X, may have something to do with it, would you
18 ask for data preclinically that would be in biomarker X
19 positive and negative before you give this designation
20 for pancreas overall?

21 DR. LEWIS: I think that, that was an element
22 of the question. Should, should we be asking -- when

1 we are familiar with this mechanism of action, should
2 we be asking those questions or do we confine ourselves
3 to the pancreatic cancer?

4 DR. KUMMAR: So my two cents would be, yes, I
5 think you should ask because if there is no evidence of
6 biomarker negative that they have generated, their, all
7 their activities actually in biomarker positive
8 pancreas, then I think either they need to go back and
9 generate for negative or just develop it for the
10 positive. It shouldn't go to patients without some
11 evidence to say that it has activity in biomarker
12 negative. So I think asking that question's valid at
13 that point.

14 DR. MOSCICKI: Well, yes, but I don't know
15 that we should force sponsors who have reason to
16 believe that pancreatic cancer in a clinical trial will
17 respond to suddenly now redefine their approach that,
18 and you know, for, who knows? Maybe the biomarker X is
19 a propriety test and are we suddenly going to say now
20 you've got to go do a proprietary test even though
21 you've shown us that, in fact, it works in pancreatic
22 carcinoma?

1 So, you know, I would be careful about saying
2 that you should mandate testing in that scenario.

3 DR. SUL: I mean I think though at the same
4 time it could be a little artificial to, to ignore the,
5 the data that's out there about the mechanism of action
6 and, and, you know, the effectiveness of the product.
7 So, at the same time I think it would be okay to
8 consider, you know, asking the sponsor for a rationale
9 for why they feel that it wouldn't necessarily apply in
10 the biomarker positive all-comers population.

11 You can ask, you know. They don't -- you can
12 ask just because I think it's, it's also, you know,
13 it's also a way for you to indicate for the, for the
14 office to indicate that you're aware of, you know, what
15 these implications are and how these products are, are
16 working.

17 DR. LEWIS: Question?

18 MS. HOLLOWAY: I have a question. I'm Jamie
19 Holloway. I'm a patient advocate. And so I think
20 that the, I think I would agree completely with Dr. Sul
21 that you can't ignore the science that's already there
22 because perhaps in pancreatic cancer or whatever your

1 rare disease is, you just have a higher prevalence of
2 this biomarker.

3 And so you're maybe seeing overall a good
4 result, but really it's just a really good result in
5 the positive people and not a good result in the
6 negative people. But by putting them in this group,
7 now you're treating the negative people who should be
8 treated otherwise.

9 And so you're, I think you need to at least
10 look at the biomarker if you know that that's going to
11 be important in the mechanism of action. And if, and
12 if you look at it and you can say, okay, it's not, then
13 that's fabulous.

14 But if it's, if it's clear delineation, I
15 think that's something really important for the patient
16 population when they're making treatment decisions.

17 DR. LEWIS: Thanks.

18 DR. MOSCICKI: So in that case you would make
19 -- let, let's say that the clinical trial was conducted
20 without access to the biomarker assay, so there's no
21 data on the biomarker in those pancreatic cancer
22 patients. Yet you know that the product works in the

1 clinical trial, now are you going to make the sponsor
2 go back and do another clinical trial in which, and,
3 and make, you know, patients wait with pancreatic
4 carcinoma another year or two for that other clinical
5 trial to be done with the biomarker?

6 DR. SUL: Hopefully the review division will
7 have given the advice prior to the, to the trial being
8 underway.

9 DR. MOSCICKI: I know, but we're in this
10 hypothetical situation.

11 DR. HONG: And that hypothetical situation, if
12 you're seeing activity in, in patients, irregardless of
13 the biomarker, then you have a strong, you know --

14 DR. RUBIN: Yeah, and it just goes back again
15 to where if the circle's separate from the square or
16 not, right? I mean if the circle's separate from the
17 square and you've got activity, it's pretty simple,
18 right? You know.

19 DR. STARTZMAN: But understand that the orphan
20 drug designation does not determine who you're studying
21
22 this in. You don't, if you get orphan drug

1 designation for pancreatic cancer, you can then
2 determine whether or not they're positive for the
3 biomarker and, and enroll patients positive. Or you
4 can, you know, it's, it's up to you how you're going to
5 develop it.

6 DR. MOSCICKI: Yeah, if you have that ahead of
7 time, but, you know, that was not the scenario
8 presented here, right? So, I'm just saying that we
9 should be careful about demanding information that
10 doesn't exist if it doesn't exist.

11 MR. KARST: I think it's worth pointing out.
12 I mean all the scenarios here we've, we've looked at
13 the red circle and the blue box. But there are
14 potential issues lurking if you get rid, rid of the red
15 circle. So, do different biomarkers, groupings of
16 biomarkers, constitute different diseases or conditions,
17 right?

18 So, two, versus three, versus, you know, four,
19 you may add on over time. Assuming they are different
20 diseases because they're, they're different biomarker
21 groupings, presumably you'd have to seek separate
22 orphan drug designations for each, you know, added

1 biomarker. And then if you get these staged approvals
2 over time, there is at least, I think from the generic
3 perspective, there is a possibility of multiple
4 seriatim periods of orphan drug exclusivity.

5 And it does occur in the oncology space right
6 now where you're approved first for third line, then
7 get second line, then you get first line. And each
8 time you get a period of orphan exclusivity and there
9 are, of course, labeling issues for, for generics in
10 terms of the labeling of the brand changes. And then
11 how does the generic get approved?

12 I know FDA's dealt with that recently in the
13 context of bortezomib, but it seems like it's also
14 potential here just within the, the blue square there
15 where there could be staged approvals over time,
16 multiple seriatim periods of exclusivity, and suddenly,
17 you know, generic drug manufacturers faced with the,
18 the issue of how do you adequately label the product
19 given that the brand now has new labeling.

20 DR. LEWIS: It does bring us to the question -
21 - we've talked about designation so far and how we
22 should designate. We can take a few questions, but

1 then I think we'll save the exclusivity part 'til our
2 after lunch. It might be a bit much to try to move
3 into that scenario now.

4 But I do agree the exclusivity issues are some
5 of our most tricky to think about. And areas, depending
6 on your philosophical look at the designation, that may
7 influence your exclusivity perspective as well. But
8 perhaps we can take a question or two from the audience
9 before we break for lunch in about five minutes.

10 ANGELA: I'm Angela, Angela. No financial
11 disclosures. My question would be, what is it about the
12 current Orphan Drug Act that has prohibited us from
13 getting to this point anyway? Without any new change
14 or programs or legislation, what was it that prevented
15 the current Act from moving forward to get new drugs
16 adopted in the small markets?

17 I mean that's what it was intended for anyway.
18 And there seem to be a lot of financial incentive that
19 if you open up new markets, you get paid more money.
20 Your research is rewarded in a number of different
21 ways. So what was it about that incentive or the
22 program that failed?

1 DR. LEMERY: I don't think we're saying that
2 there's a failure here. We approved, you know, BRAF
3 mutation positive anaplastic thyroid cancer based on
4 fewer than 30 patients. So I don't think it's a
5 failure of the Act. That's not why we're here. We're
6 here to discuss how to apply the act given the, given
7 these new approval considerations. You know, we
8 approved the pembrolizumab.

9 Approval for tissue agnostic, you know, there
10 are, there are patients in there that have, you know,
11 very few tumor types studied, so this brought the drug
12 to the market for patients much faster than would have
13 done, I mean exponentially faster, than would have been
14 done under a traditional paradigm where you have to study
15 each disease separately.

16 So I think there's not a failure here. We've,
17 we've clearly moved faster on some of these than, you
18 know, than anyone would have ever expected. This is
19 just a new way to apply the law, which is not
20 necessarily written for sort of modern day science.

21 DR. LEWIS: And I think that that is right.
22 We've been really excited to be a part of this time

1 when there is so much advance going on and we've been
2 able to take advantage of that in so many ways. And
3 that's why we've had so many records in approvals and
4 just very exciting lifesaving therapies coming forward.

5 What we're trying to do now is we have moved
6 forward just as, as you were saying. We have
7 designated. We have approved. We have provided
8 exclusivity, but it's not ever a bad idea to self-
9 examine, to take a look and see what is it that we
10 could do better.

11 But as we've heard, people think we have these
12 Tools, and we're now excited to hear from you about
13 different ideas about how to do this better, both in
14 the designation phase and exclusivity phase. And you
15 may actually, we might end up right where we were in
16 these two or three that we've done.

17 But I do agree it's, it's really, actually an
18 exciting time to be implementing the Orphan Drug Act
19 and the tools that it's given us and to developers
20 have been terrific, so.

21 DR. HONG: I, I agree with Steve and Deb here.
22 I don't think it's the limitation of the law up to this

1 point. To a large extent it was kind of the structure
2 of, of oncology in a way and, and the science. I mean,
3 you know, if you think about, you know, kind of
4 biomarker driven science, it's not like we've been
5 doing this since 1943. This is really since the early
6 2000s that has, and it's really exploded in the last
7 several years.

8 And I, Joohee said that she can't imagine, you
9 know, doctors not treating like breast or pancreatic.
10 But, you know, to be honest with you, I, I run a clinic
11 where people send me patients not because I'm a GI
12 expert, which I have an interest in, but really because
13 I run a trial that, that is NTRK and I have, and I have
14 the most experience in our, in our group on these NTRK
15 fusion patients across histologies.

16 Likewise, there are other folks in my group
17 who are immunotherapy experts and they get, see all
18 different types of patients because they, they know how
19 these drugs work and they know how they work in these
20 patients who have metastatic refractory disease.

21 So there is -- I think there is a feasibility
22 in the future that we will be treating patients as, I'll

1 be an NTRK fusion doctor or whatever, you know. But
2 less so of that -- probably in the metastatic scene, less so
3 in the earlier settings, but --

4 DR. LEWIS: And we want to keep, we want to
5 keep aligned with that. That's probably what we're
6 hearing most about here, is as the Orphan Drug Act
7 moves forward, as orphan products move forward, we want
8 to maximize the use of these tools. And so that's why
9 we much appreciate people coming with their different
10 perspectives on helping to do that. And we have
11 another question from the audience.

12 MS. HOLLOWAY: Okay. So I, I'm curious. I
13 think obviously it seems like we're going to be moving
14 towards having a lot more of these orphan designations
15 and sort of by definition you're getting smaller
16 populations. So, I'm curious if anybody has any
17 thoughts about considerations or experiences with how
18 to do a clinical trial when you're already starting
19 with such a small population to begin with?

20 And you mentioned, you know, an approval based
21 on a small number, but I'm wondering if there are
22 considerations for remote possibilities so that

1 geography isn't going to be a barrier to accumulating
2 enough patients to perform a trial?

3 DR. LEMERY: Eric, have you, have you done
4 just, you know, just-in-time enrollments? I know some in industry
5 have done different ways to sort of foster, you know,
6 quick, quick opening? I can also say that we've worked
7 in a few cases with companies where, you know, with
8 compassionate use, often it's the, the, the
9 investigator who requests it and you don't get much
10 information.

11 But like for drugs that have really been seen
12 as, they're really active, really are in development,
13 we've worked with companies that say, you know, maybe
14 you should submit those to your own IND and collect,
15 you know, basic information regarding that patient.
16 And those have fostered, you know, help foster
17 applications in some cases.

18 So I think, you know, we do recognize that,
19 you know, a patient in New York is going to have, or
20 Houston, a much easier access to a trial than, you
21 know, you know, a small town in Iowa or Montana. So,
22 but there are different mechanisms. And I know

1 industry has worked in different ways to, to do this as
2 well.

3 DR. RUBIN: Yeah. And I think there are also
4 an increasing number of databases where, you know, many
5 people at the time of diagnosis they're, they get a
6 test, an NGS test or something that really gives a
7 pretty board profile of, of their disease. And that's
8 kept, that's accessible later on. So that if, you
9 know, down the road a new drug comes along and it
10 happens to match with a particular mutation they have,
11 you can find that patient. And consent's allowed so
12 that they can be contacted and they can be put onto the
13 trial.

14 MS. GAVIN: We're also working with patients,
15 patient organizations and disease states early on to
16 help them establish natural history studies so that
17 they're coalescing communities together. And we're
18 also excited to be working with some companies who are
19 looking at subsets, creating a subset study within a
20 study whereby, where we're basically joining that
21 natural history study with some of their pre, pre-early
22 clinical designs.

1 So we think that will also help because we, we
2 in the natural history studies, we, we go to patients
3 where they are, where they live.

4 DR. MELLIS: Yes, the natural history studies
5 are so pivotal, but they can also be integrated with
6 biomarker assessment and biomarker collection and
7 really having patients ready to go when a protocol
8 and/or therapeutic might be available or a candidate
9 therapeutic might be available for testing.

10 It also brings up the topic of master
11 protocols that Dr. Gottlieb mentioned earlier in the
12 day. Those, those are going to be so instrumental in
13 helping enable remote enrollment and, and the
14 evaluation of multiple therapeutics.

15 DR. LEMERY: And in some cases like NCI, I
16 think NCI-Match has actually had a lot of sites that
17 aren't necessarily at your MD Andersons and, and Sloan
18 Kettering, they are at, you know, smaller sites. And
19 hopefully that helps, but, you know, clearly there's,
20 there is a need especially with, you know, you take,
21 you know, NTRK, for example, which, you know, it's,
22 these, at least they're --

1 We don't know the exact prevalence, but it's
2 not easy to find a patient with an NTRK fusion in a
3 lot of cases because patients aren't just being tested.
4 So I don't know if you have experience with patients
5 traveling and how that's been facilitated to --

6 DR HONG: So, so the trial has, the company at
7 least have been working with, Loxo, has been very
8 accommodative in trying, in getting patients. They
9 recognize these patients are rare. So they've been
10 accommodating in that, getting patients if they're
11 identified in the community, whether they're from, you
12 know, California, whatever to, to our center or sites
13 that are running these trials.

14 So, but I, I do agree that we can definitely
15 improve whether through master, master trials or some
16 other ways to try to get these drugs out in the
17 community. And one, and one question I have, which I
18 know this is probably a whole new topic, is this right,
19 right to use issue that's going to come up, I'm sure,
20 at some point and how this affects the orphan drug, or
21 orphan drugs and, you know, I'm sure that's a whole --

22 DR. LEWIS: Yeah. It is actually a different

1 topic, but, but what I, what I would suggest is that
2 there is a lunch hour right now. So we can, we can
3 take a break from our conversation. If we can
4 reconvene then at 1:30. We have about 45 minutes more.
5 We'll talk about exclusivity and we'll also focus a lot
6 if folks have additional input and questions from the
7 audience, we'll try to work a little bit on that.

8 I really appreciate everyone's attention and
9 patience with everything this morning. If you have any
10 suggestions, please do come up and let us know.
11 Otherwise, we'll reconvene at 1, 1:30. Thanks very
12 much.

13 LUNCH

14 DR. SUL: Okay. So I think we have almost
15 everyone back here up here on the panel. So I think
16 we'll go ahead and get started with the, the second
17 panel discussion with involvement from the audience as
18 well. We welcome the audience to participate. When
19 you come up to the mic, please, as we've heard all
20 morning, please speak closely to the mic and please
21 state your name and, and where you're from.

22 And so this afternoon I think we're going to

1 move on a little bit away from the, a little bit away
2 from the designation, still related, but talking a
3 little bit about exclusivity. And we've heard all
4 morning about how we should have as many incentives as
5 possible and that incentives are good. But I think
6 sort of the, the corollary to that is that, you know,
7 what are the implications of these incentives. So what
8 comes with these incentives and, you know, part of that
9 is exclusivity and how that might impact drug
10 development.

11 So we're going to move on to the exclusivity
12 questions and I'll turn it over to Debra.

13 PANEL DISCUSSION WITH AUDIENCE Q&A

14 TOPIC THREE

15 DR. LEWIS: Thanks everyone for coming back on
16 time and we're able to, to move along. As Joohee said,
17 we're going to move to exclusivity. I think that folks
18 can feel welcome as questions do arise to come to the
19 microphone and, and raise a question. But we also did
20 have some prepared scenarios.

21 Again, it brings us back to some of the
22 specifics. We know that we're not going to know every

1 scenario, but what we learn from this is your input on
2 some of these principles. It helps us. We can see
3 right away about how people address these questions in
4 ways that will help us.

5 We also do have some questions that we'll try
6 to intersperse from our folks who are webcasting with
7 us today. But I could start I think with our Topic 3
8 on exclusivity.

9 And this question is up on the screen now and
10 it's about discussing how FDA should determine the
11 scope of orphan exclusivity when a drug receives
12 marketing approval for a non-orphan tissue agnostic
13 indication. For example, a prevalence that's over
14 200,000.

15 So it might help you to think about this
16 perhaps as like the MSI-high. That's a situation
17 wherein the blue box, it receives approval, but then
18 the same drug subsequently receives marketing approval
19 for histology specific indication. And then that
20 indication had received orphan drug designation. And
21 again, we're sticking with our example of pancreatic
22 cancer. Its indication, its disease in designation was

1 under 200,000. The indication, we're just using
2 pancreatic cancer in general.

3 How should we provide marketing exclusivity
4 for that pancreatic cancer approval if it's got a great
5 overlap with the, with the already approved tissue
6 agnostic that was not rare, that's over 200,000? So in
7 this case you've had a non-rare and now coming into it
8 an approval. Should that exclusivity overlap? Is it a
9 different disease as was suggested by some?

10 And so this question is one that helps us
11 understand a principle and we just appreciate your
12 thoughts on how we approach that.

13 DR. HONG: Can I ask a couple questions about
14 the scenario?

15 DR. LEWIS: Please do.

16 DR. HONG: So, so we're assuming that, one,
17 that the pancreatic cancer indication, you know, one,
18 went through this FDA office, had good clinical trials
19 that suggested efficacy, etc., enough that you guys
20 felt that this would indicate a true orphan indication,
21 and, and assuming this was irregardless of the
22 biomarker. The biomarkers were not necessarily a part

1 of that trial or, or the development in a sense.

2 DR. LEWIS: So at the designation stage, which
3 may have been very early, may have even been before the
4 tissue agnostic characteristics were recognized. I'm
5 going to assume that just for a moment, just it could
6 be different, different aspects to it. But we don't
7 require a whole clinical trial. As we talked about
8 before that, that level of evidence.

9 We, we love to have clinical experience, but,
10 yes, you can assume that the evidence was sufficient
11 for designation of that pancreatic cancer indication.

12 DR. LEMERY: A better way to simplify things,
13 and please correct me if I'm wrong, just to say like
14 this example is you have, you know, Drug X is approved
15 for the tissue agnostic and then you have the second
16 approval. So, I'm a generic company and I want to come
17 in and I want to get approved for biomarker positive
18 cancer.

19 So would, and your question I think in the
20 scenario is would the generic be approved for biomarker
21 positive cancer or biomarker positive cancer except
22 biomarker positive pancreatic cancer? Is that sort of

1 what you're getting at? So that's what I just wanted
2 to clarify for the audience.

3 MR. KARST: So it seems, I mean if, if they're
4 different diseases, right, the biomarker X versus
5 pancreatic cancer, the exclusivity runs to the
6 indication for the drug, pancreatic cancer.

7 Seems to me it's a very easy carve out if
8 you're going to, if you're viewing this through the
9 paradigm of the indication and the disease or condition
10 here that's been designated, that it's an easy carve
11 out and generic can get approved for the biomarker X
12 population.

13 DR. LEWIS: So by carve out you mean that
14 you're looking at those as an overlap of the approvals?

15 MR. KARST: Correct. So let's say biomarker X
16 is approved today and pancreatic cancer's approved
17 three years from now, right? So generic comes in and
18 you've got the orphan exclusivity on the pancreatic
19 cancer indication extending out. They'll just omit
20 that distinct indication from their labeling, again,
21 under the rubric that biomarker X is a distinct disease
22 or condition that's indicated in the labeling and

1 pancreatic cancer is a distinct disease or condition in
2 labeling.

3 DR. MOSCICKI: And that position would be
4 consistent with the principle that we outlined at the
5 beginning where you would give exclusivity just for the
6 pancreatic cancer indication. And otherwise it gets
7 really convoluted when you start looking at
8 overlapping, testing, the issues that came up over
9 whether, where does the test positive/negative,
10 now/versus later, all that gets in the way of trying to
11 make a crisp decision. And in the end we end up with
12 data that we've been looking for in pancreatic
13 carcinoma related to this.

14 DR. STARTZMAN: Yes. The alternative would be to,
15 to give exclusivity just for pancreatic cancer that's
16 biomarker negative --

17 DR. MOSCICKI: Right.

18 DR. STARTZMAN: -- because it's already approved
19 for, for biomarker positive tissue agnostic, which
20 would include pancreatic cancer that's biomarker
21 positive.

22 DR. MOSCICKI: Yeah, but I'm not sure what the

1 legal argument for that really is because if the
2 clinical trials didn't particularly differentiate on
3 that basis, then I'm not sure how you would try to do
4 that. So I, I just say it's always just cleaner to say
5 that that's what, if that's what the clinical trial
6 studied, if that's how the patients were identified,
7 then that's how you should act.

8 DR. KUMMAR: Well, the problem with the whole
9 scenario, it goes back to the fact that if the trial
10 was done without the biomarker being incorporated in
11 it, you don't know that the activity that's being shown
12 is all driven by the biomarker positive population.
13 And so, I mean on the surface it's, I think it's in
14 theory to just say, okay, the exclusivity is for
15 pancreatic cancer only. And it starts from when you
16 approve a pancreatic cancer, but I don't know how you
17 approve it without knowing the biomarker when you know,
18 when you put it in context of what the existing
19 knowledge exists, right?

20 DR. LEWIS: Mm-hm.

21 DR. KUMMAR: So, and again, to the point that
22 was brought up earlier, is that I don't know if

1 necessarily in that situation it's fair to the patients
2 that are biomarker negative to be treated with a drug
3 that hasn't -- to be -- or a drug on the market that
4 hasn't shown activity in that population. What if all
5 of it is driven by the biomarker positive and we are
6 actually claiming to the patients that you have an X
7 percent response rate from this drug in this disease
8 which we don't know, right?

9 So I don't know how, and if you know that
10 there is biomarker activity, how do you actually
11 approve without knowing the biomarker in the clinical
12 trial?

13 DR. LEMERY: I, I guess the only thing I would
14 mention there is, is that that's more of a scientific
15 discussion that would be had with review teams and the
16 companies about the basis for approval and whether that
17 biomarker has to be assessed within the clinical trial,
18 you know. And we, we would have to assess whether the,
19 the effect is completely driven by patients with a
20 biomarker. It's probably less of an exclusivity issue.

21 DR. SUL: Yeah. I, I would agree with that
22 and I think that's why it makes it, you know, really

1 difficult to have these carve outs within a disease.
2 And also, if you think about it, you know, if, if the
3 sponsor -- let's say in this scenario that the
4 sponsor's developing the drug for pancreatic cancer
5 after they've already gotten the, the original
6 indication, approval for the original indication, and
7 they're developing it knowing full well the biomarker
8 positivity and potentially, you know, capturing that
9 data in the study and seeing, well, look, they, there are
10 responses across the board for whatever reason, you
11 know, whether you're biomarker positive or negative,
12 there's responses across the board because there's
13 something about pancreatic cancer where this drug is,
14 is, has activity, you know.

15 And, and I think in that case the, the drug
16 development really was in that disease and therefore
17 that's really where the exclusivity lies. And it would
18 be almost artificial to carve it out just for the
19 biomarker negative population.

20 DR. KUMMAR: No. I think the scenario you
21 present where they're looking at both populations and
22 showing activity and you're convinced with the data, I

1 think it's straight forward that you should probably
2 give it to pancreas and then the exclusivity. It's
3 when the biomarker's not being assessed, that's when
4 the problem is.

5 DR. SUL: Yeah. And, and I think again that's
6 more of a review issue within, you know, the review
7 division rather than something that the, that the
8 Office of Orphan Products would determine.

9 I mean certainly if they had a question about
10 is it possible that the, the response or the activity
11 is driven by a specific population, they would bring
12 that to us and hopefully we would have, you know, have
13 that same question.

14 DR. STARTZMAN: And, and I think one thing
15 that needs to be understood is when we designate, you
16 know, we designate something, the exclusivity goes to
17 the first sponsor to get approval. And that's why in
18 this case the, the sponsor got approval previously for
19 this tissue agnostic, which includes a portion of
20 pancreatic cancer patients.

21 And that's why when pancreatic cancer
22 subsequently gets approved, there is, there are those

1 who would think you should carve out the part of the
2 pancreatic cancer that already has an approval from
3 that drug unless they can demonstrate superiority, in
4 which case they could get exclusivity of the whole
5 thing. If you consider them separate diseases, then
6 there's no problem. You just give exclusivity for
7 pancreatic cancer.

8 DR. MOSCICKI: So you'd have to demonstrate
9 clinical superiority for the same drug, against the
10 same drug.

11 DR. STARTZMAN: In order to get exclusivity.

12 DR. MOSCICKI: Right. Great incentive.

13 DR. LEMERY: And, I mean on the flipside, it's,
14 I mean ultimately I don't know how much it, it, it
15 matters because the generic company will still be able
16 to market for the biomarker. So, it, it doesn't really
17 matter at the end of the day for this example.

18 DR. LEWIS: So no additional discussion on it,
19 and if, if I'm hearing, is there, I, it's very clear
20 your suggestion is that, the fact that they, that there
21
22 is a previous approval for that same drug for those

1 same patients, we should consider it as just a
2 different disease. Anybody have any, any other aspects
3 on that?

4 DR. HONG: It sounds like a lot of our debate
5 is going back to what Steve was mentioning, what is
6 disease, and in the context of biomarker what is
7 disease?

8 DR. LEWIS: Mm-hm.

9 DR. HONG: And I think in, in this, in this
10 context with regulation and how we sparse out things
11 like orphan designation, exclusivity, then we really
12 need to have a, you know, since this, since this notion
13 of biomarker disease is really truly a new entity, we
14 really have to have, I would argue a high bar about
15 what that is.

16 And that entails a lot of what, you know, and
17 you guys have a perfect model of this, I think, with
18 the, with MSI-high disease, that there seems to be
19 uniformity, not necessarily across every single tumor
20 type known in existence, but at least a uniformity in
21 quote, "many," and you can define many as however you
22 want, across many different histologies. And that

1 there is a truly predicted biomarker and then you
2 define that as, as kind of a separate disease.

3 But I think that bar has to -- however you
4 guys want to define it, has to be a little bit higher
5 than just saying, oh, you know, they, there's some
6 similar characteristics across these different tumor
7 types.

8 DR. LEMERY: I think that would be more a
9 review issue bar and maybe orphan designation
10 considerations of with -- I know we've some
11 discussions, but I think it's --

12 DR. LEWIS: Oh, move into the mic.

13 DR. LEMERY: I think exclusivity, I think
14 exclusivity it may not be, you know, 'cause here
15 you're, you've already given orphan designation and
16 you're, you know, deciding what, you know, what
17 indication you give exclusivity for.

18 DR. MELLIS: Another point is it, it's
19 possible that the tissue agnostic indication that came
20 before might not have included examination of
21 pancreatic cancer specifically. And in this, in the
22 second instance, this development program for the

1 orphan indication of pancreatic cancer is a lot of work
2 and it's providing a lot of useful information to the
3 field. And it's going to be of benefit to patients and
4 it's essentially an innovative endeavor. So I, I would
5 hope that incentives would be maintained to encourage
6 that.

7 DR. LEWIS: Okay. With that I'm going to, I'm
8 going to go to our Topic 4, which is, oh, Topic 3B. We
9 have another piece to this. I'm sorry. So we're still
10 in the same scenario. We have Drug A receiving market
11 exclusivity. Oh, this is a little different. Drug A
12 is receiving market approval for pancreatic cancer.
13 It's a histology specific, but Drug A has orphan
14 designation for all cancers that are tissue agnostic.

15 So, I think what we have some idea where this
16 discussion may go, but for us it was still -- we still
17 receive so much input that we consider grouping and now
18 it sounds like we're very much into splitting. But it
19 would be helpful to us if you could discuss whether
20 Drug A should receive exclusivity only for the, the
21 biomarker positive pancreatic cancer or, or should get
22 broader.

1 DR. MOSCICKI: So I think we need a, a little
2 clarity on this example, though. And for pancreatic
3 cancer indication it says it received marketing
4 approval, but it didn't say that it, that, that was,
5 that it had orphan drug designation prior to that
6 market approval or not. So did it or didn't it? In
7 other words, does it now have, did it have orphan drug
8 designation? Is, is it a -- does it have exclusivity
9 for the first approval?

10 DR. LEWIS: Does the pancreatic cancer
11 indication have --

12 DR. MOSCICKI: Yeah. So, I, I read this, that
13 you have marketing approval that was established for
14 the drug in pancreatic --

15 AARON FRIEDMAN: It has
16 designation for the biomarker, the blue box.

17 DR. MOSCICKI: Yes. But, not --

18 AARON FRIEDMAN: But it's
19 approved --

20 Dr. MOSCICKI: -- for pancreatic cancer.

21 AARON FRIEDMAN: -- for the red
22 circle.

1 DR. MOSCICKI: The red circle has no orphan
2 drug exclusivity --

3 DR. LEWIS: That's right.

4 DR. MOSCICKI: -- assigned to it.

5 DR. LEWIS: That's right.

6 DR. MOSCICKI: Okay.

7 DR. LEWIS: It's only, it's --

8 DR. MOSCICKI: That, that's an important piece
9 of clarity.

10 DR. LEWIS: It is. It is. Mm-hm.

11 DR. MOSCICKI: Yeah.

12 MR. KARST: But in that
13 case, I mean it seems --

14 DR. LEWIS: So we're really looking at what's
15 the scope then of the exclusivity. Since it has the
16 designation for the tissue agnostic, it has approval,
17 it has approval for the pancreatic, but not necessarily
18 any designation or, or therefore any exclusivity.

19 DR. MOSCICKI: Yeah. So I, I know this is
20 going to sound odd coming from me, but, but again, I,
21 I, I still think incentives are important to maintain
22 and given that the new indication for biomarker

1 positive solid tumors has the orphan drug designation
2 and that does include pancreatic carcinoma, you know,
3 in, in that there was no other competing issue with
4 that, then it seems like you would include that
5 population in the new orphan drug designation.

6 DR. LEWIS: That, that is interesting given
7 that we were looking at them as very different.

8 DR. MOSCICKI: I know. I know. I know.

9 DR. LEWIS: Mm-hm.

10 DR. MOSCICKI: Yeah, so that's kind of --

11 MR. KARST: It, it seems if we're following
12 the, the paradigm of what is the disease or condition
13 here that, and if you have designation for the
14 biomarker that is the disease or condition and you
15 obtained approval for a different disease or condition,
16 which is pancreatic cancer, so the, it would,
17 consistently with what we've been discussing there,
18 there simply shouldn't be any exclusivity in this
19 scenario because it's a different indication than that
20 for which you have orphan designation, at least in this
21 case.

22 DR. SUL: So --

1 DR. MOSCICKI: That would be true to my
2 previous principle.

3 MR. KARST: Yeah. That's true.

4 DR. LEWIS: But, not, but, yes, so that --
5 just so we're clear on that, you're, you're staying
6 consistent with that --

7 MR. KARST: Correct.

8 DR. LEWIS: And you're talking about the, the
9 incentive perhaps --

10 DR. MOSCICKI: Yeah. I think the order in
11 which this occurs is what I, I'm sort of thinking here.

12 DR. LEWIS: Right.

13 DR. MOSCICKI: And why I departed a little
14 from that principle and --

15 MR. KARST: It, it might be in the way the
16 question is worded. Where it says Drug A has orphan
17 drug designation for all cancers that are biomarker X
18 positive. But the designation really wouldn't be for
19 the cancers, right? It's for just the biomarker
20 positive tissue agnostic disease?

21 DR. MOSCICKI: Oh, oh, I see. Yeah.

22 MR. KARST: Right? So they don't actually

1 have the designation for the cancers. It's for the
2 biomarker.

3 DR. MOSCICKI: Yeah. And it says it's for
4 only biomarker X positive pancreatic carcinoma. Is
5 that true? You're not --

6 DR. LEWIS: So --

7 DR. MOSCICKI: -- going to include the other
8 solid tumors in the --

9 DR. SUL: I, I think the other clarifying
10 point about this, this question also is, or, or this
11 scenario also, is that, that the approval is only for
12 the pancreatic cancer.

13 MR. KARST: Right.

14 DR. SUL: You know? So --

15 MR. KARST: They never approved it --

16 DR. SUL: Yeah. They never approved it for
17 the biomarker --

18 DR. MOSCICKI: Right, right.

19 DR. SUL: -- positive --

20 DR. MOSCICKI: Right.

21 DR. SUL: -- tissue agnostic.

22 DR. MOSCICKI: No, no. I understand that.

1 DR. SUL: Yeah. But the, the designation is
2 there. So, I think that's where the, the question is.

3 DR. MOSCICKI: But, but the second part says
4 whether Drug A should receive orphan drug exclusivity
5 for only biomarker positive pancreatic cancer and not
6 other solid tumors?

7 DR. SUL: Because it's only approved for --

8 DR. LEMERY: It wouldn't get exclusivity if
9 it's not approved for the --

10 DR. SUL: Yeah.

11 DR. LEMERY: -- for the use, right?

12 DR. MOSCICKI: Right. But it, it doesn't sort
13 of say --

14 DR. SUL: I think, I think the question is
15 should it get --

16 DR. MOSCICKI: I'm really struggling with what
17 --

18 DR. SUL: -- exclusivity for --

19 DR. MOSCICKI: What did it get approved for?

20 DR. STARTZMAN: Take the --

21 DR. SUL: Pancreatic, all, all-comers.

22 DR. MOSCICKI: And it never got approved for

1 the other solid tumors.

2 DR. SUL: Exactly.

3 DR. MOSCICKI: Oh. Yeah. Well. Okay.

4 The answer is it should only be for the biomarker X --

5 DR. MELLIS: Question. If, if a drug has been
6 approved already and is on the market for a rare cancer
7 indication like pancreatic cancer, could it
8 subsequently receive orphan designation and exclusivity
9 after the approval has been completed?

10 DR. LEWIS: If, if I understand the question,
11 once something is approved, the same drug for the same
12 indication, we will not designate that after that
13 unless there's a, a plausible hypothesis for
14 superiority. And --

15 DR. STARTZMAN: Yeah. Unless, unless the
16 sponsor submitted the request for orphan drug
17 designation prior to the submission of the market
18 application.

19

20 DR. LEWIS: Yes.

21

22 DR. STARTZMAN: They could submit prior, but

1 not get designated until after the approval.

2 DR. MELLIS: Oh. I see.

3 DR. STARTZMAN: In some unusual --

4 DR. LEWIS: Mm-hm. Yes. We've had that --

5 DR. STARTZMAN: -- situations.

6 DR. LEWIS: -- that situation where it takes a
7 while. They submit the, the, their designation and
8 then they get approved and the designation actually
9 occurs later. But those are, that's an unusual
10 situation.

11 DR. MELLIS: So. Okay. Thank you.

12 DR. MOSCICKI: So the other thing, piece of
13 information then was that the data failed to show that
14 it fulfilled the needs of a, a tissue, tissue agnostic
15 indication.

16 DR. LEWIS: Not necessarily.

17 DR. HONG: And this -- well, I, I think I
18 understand the question.

19 DR. MOSCICKI: But isn't that key to whether
20 you get market exclusivity --

21 DR. SUL: So, so I think this is sort of an
22 indication of how --

1 DR. MOSCICKI: -- whether it --

2 DR. SUL: -- complicated the issues are.

3 DR. MOSCICKI: -- failed or didn't fail.

4 DR. HONG: So what you're saying is, is the
5 pancreatic indication was approved --

6 DR. MOSCICKI: Yeah.

7 DR. HONG: -- and then you have a designation
8 for kind of tissue agnostic biomarker. So, the question
9 is then even though -- so now that you have a
10 pancreatic indication that's approved, should then the
11 biomarker X pancreatic tumors also get a drug
12 exclusivity? I, in my opinion, no. I think you have
13 to wait until the biomarker X positive solid tumor --
14 because, you, you don't know entirely whether or not,
15 you know, what is truly driving the, the, you know, the
16 approval in the pancreatic, right, if you haven't
17 gotten the biomarkers in pancreatic.

18 DR. MOSCICKI: Yeah. I think it's all data
19 based here. It's -- this is, this is where you do have
20 to have data.

21 DR. SUL: Yeah, and I --

22 DR. MOSCICKI: Principles aside, I would say

1 then the principles stand that the answer is no unless
2 you have data.

3 DR. HONG: You agree with me.

4 DR. MOSCICKI: Huh?

5 DR. HONG: You agree with me.

6 DR. MOSCICKI: I do.

7 DR. HONG: Oh, my God.

8 DR. MOSCICKI: And, yeah, that, that, by those
9 principles this would be no. But it -- unless the data
10 was very clear --

11 DR. HONG: Yeah. I agree.

12 DR. MOSCICKI: -- that it was -- showed
13 biomarker X positive pancreatic carcinoma efficacy.

14 DR. SUL: Right. And so then in this scenario
15 then there would be no exclusivity because the sponsor
16 had not prior to the marketing application received
17 orphan designation for pancreatic cancer.

18 DR. MOSCICKI: I can buy that.

19 DR. SUL: So, yeah. Okay. So I think that's,
20 that's the clarification, you know, we wanted to make.

21 JAMIE HOLLOWAY: So thank you for clearing
22 that up 'cause that was my confusion. So I think the

1 distinction between disease and indication is
2 important. But it's also important to remember that in
3 the overlap of the red and blue in there is like
4 people, right? And so the thing that could be
5 difficult is if you have a pancreatic cancer patient in
6 the red bubble who is on the drug and depending on the
7 timing of this they get moved to the bottom half of the
8 bubble and now they're in the orphan drug designation.

9 So, it could very potentially be that a drug
10 that they had access to at a more reasonable rate is
11 going to be more expensive because they're not going to
12 have the generic option because now they're excluded,
13 or they're part of the exclusivity bubble. And so, I
14 mean it's a very, it's a very fine line and I'm glad
15 that there's a multi-stakeholder discussion because I
16 want drug development for rare cancers, but I also want
17 patients to get the drugs in the end.

18 But I think just considering that the overlap,
19 there's people in all of those overlaps, and that, you
20 know, it's going to, it's going to affect their access
21 to the drug. And it seems, it seems cruel to say we've
22 done some new research so now you, you don't get

1 generic even though your, your buddy over there in the
2 other half of the bubble gets the generic drug. So,
3 that's just something that I would hope that we could
4 at least consider as the discussion goes forward.

5 DR. LEWIS: It, it's at forefront of all of
6 our, of our thoughts about the people who are being
7 affected by this. So, I appreciate you bringing up as
8 we're looking at diagrams that they're representing the
9 people who have these conditions and it's well, well
10 taken. Thank you.

11 MS. GAVIN: So we don't support extending
12 exclusivity just for the sake of it. There has to be
13 benefit to the patients. I'd also make a comment on
14 generics. There's a big difference between generics in
15 the common diseases in, versus the rare diseases. At
16 least that's what the empirical data has shown to date.

17 Unfortunately, you need multiple generics on
18 the market for any measurable reduction in costs, which
19 doesn't help the rare disease community very much,
20 unfortunately, unless we can do something about it in
21 some other way, shape, or form.

22 DR. LEWIS: Thank you. I think we've covered

1 this particular scenario. I've got yet a, another part
2 of C, 3C. I think we, we still are having Drug A
3 receiving marketing approval for all cancers that are
4 tissue agnostic and the prevalence is over 200,000,
5 which means that it did not receive any designation for
6 the tissue agnostic approval.

7 But Drug A has an orphan drug designation for
8 this pancreatic cancer that's histology specific and
9 should Drug A receive marketing exclusivity for the
10 biomarker positive pancreatic cancer, that overlap
11 part? So any clarifying needed or are, are we good?

12 DR. MOSCICKI: Yeah. I need clarification
13 here too 'cause to me I, I, I'm, I need to know are we
14 defining the indication by the presence of the
15 biomarker or are we defining it by the histology of the
16 pancreatic cancer? You know, to me that, that's sort
17 of a critical question of the indication that's given.
18 And what do we really intend by that related to whether
19 or not you get exclusivity?

20 DR. LEWIS: So if your question is, are we
21 considering the -- in this particular case, the
22 designation piece is for the disease pancreatic cancer.

1 But we, we have an approval for an indication for the
2 tissue agnostic. And so our question then is does it,
3 does it cross over -- like we've talked previously that
4 the histology specific and the tissue agnostic just
5 should be considered separate and different.

6 And so that might guide you when you look at
7 this situation where the indication that was approved
8 is an indication of tissue agnostic and now we have a
9 designation for a disease, pancreatic cancer, that does
10 include the same people, the same people with
11 pancreatic positive. Should there be any exclusivity
12 given or should there not?

13 DR. MOSCICKI: Yes, but if -- I, I would say
14 if, if you came out so that the indication was defined
15 as biomarker X positive pancreatic cancer, then the
16 answer would be no. But if it, if the indication is
17 for pancreatic cancer, then the answer is yes, you
18 know, because --

19 DR. LEWIS: Don't you need clarification?

20 DR. MOSCICKI: -- then you, you know, if it's
21 really defined by the presence of the biomarker, that,
22 that's a problem, right? If that's, if you're not

1 approving it for all patients with pancreatic
2 carcinoma, but only for those that are biomarker X
3 positive, then I think you, it is the same disease,
4 right, rather than a different disease? But if it's
5 pancreatic carcinoma without, you know, necessarily the
6 biomarker, then those are different diseases and you
7 should get exclusivity.

8 DR. LEMERY: I guess there's some overlap, but
9 there, but there's, there's overlap and, you know, it
10 may depend on, on the prevalence of the biomarker and
11 the effect on, on negative. However, I think the, the
12 corollary, the important corollary is that a generic
13 could potentially get marketed for biomarker positive, X
14 positive disease, right?

15 So you still could market it for,
16 theoretically for a biomarker positive pancreatic,
17 patient with pancreatic cancer. You just can't put
18 pancreatic cancer in your, in your labeling; is that
19 correct or am I incorrect?

20 MR. KARST: I mean this scenario is just a, a
21 flip of 3, 3B. I mean it, so the answer is going to be
22 essentially the same as 3B, which is there wouldn't be

1 exclusivity because that for which designation was
2 granted. Again, assuming we're talking about the
3 disease or condition if it's the biomarker versus the
4 actual histological site.

5 You know, if there are distinct items here,
6 then they don't line up and therefore you can't get the
7 exclusivity because you didn't get approval for the
8 drug for the designated indication, or for the
9 designated disease or condition.

10 DR. SUL: And so, I mean, again I think this
11 is, this is sort of one of those situations where, you
12 know, there's the letter of the law and then there's
13 sort of the spirit of the law. So if, if the whole
14 purpose of the Orphan Drug Act is to, to incentivize
15 the development, so presumably the sponsor came in for
16 a designation for pancreatic cancer. I'm going to
17 presume before the biomarker X field had developed.

18 So they had intended to develop the drug for
19 pancreatic cancer, but then they went on to develop it
20 for biomarker X positive solid tumors, but there --
21 it's just by default because they had come in earlier
22 with the designation for pancreatic cancer that they

1 would be even in contention for exclusivity now.

2 It seems a little bit, again, it sort of seems
3 like a, a forced situation there. You know what I
4 mean? I mean it's, it's not like, it's not like they
5 went into this deciding that they wanted to develop the
6 drug for biomarker positive pancreatic cancer.

7 MR. KARST: And, and if things do change
8 during the development process, you know, they, they go
9 from, so cancer specific to, you know, agnostic, they
10 can simply go in with a new --

11 DR. SUL: Exactly.

12 MR. KARST: -- designation request right --

13 DR. SUL: Right. They would, they would have
14 come in with a different designation.

15 MR. KARST: Right. Yeah.

16 DR. SUL: And I think it would be, the onus
17 would be on the developer or on the sponsor to do that,
18 to recognize, okay, well, you know, we want to come in
19 with orphan designation at that point --

20 MR. KARST: But you could because --

21 DR. SUL: -- rather than trying to carve out
22 based on some prior designation.

1 MR. KARST: Yeah. And they'll, they'll be
2 aware of this beforehand 'cause Orphan Drugs will have
3 issued its guidance by then saying what their policies
4 are. So they'll, they'll be aware.

5 DR. STARTZMAN: Well, another issue with this
6 would be if we did grant exclusivity, would be a
7 sponsor could come in knowing that biomarker X positive
8 solid tumors is over 200,000. They could come in for
9 designation for pancreatic cancer, gastric cancer,
10 esophageal cancer, etc., you know, all these separate
11 designations.

12 And then when they get the tissue agnostic
13 approval, they would get exclusivity for the biomarker
14 X positive, all these different. So they could kind of
15 --

16 DR. SUL: Double check.

17 DR. STARTZMAN: -- get designation, you know,
18 essentially get exclusivity when, for a --

19 DR. HONG: Hopefully they won't play that
20 game, right?

21 DR. STARTZMAN: Huh?

22 DR. HONG: Hopefully they won't play that kind

1 of --

2 DR. HONG: Or is that -- so is that
3 allowed? That would be allowed under this, right?

4 DR. STARTZMAN: If, if we --

5 DR. HONG: That, is that what you're
6 trying --

7 DR. STARTZMAN: If, if we granted the exclusivity.

8 DR. HONG: It is.

9 DR. STARTZMAN: That's why keeping them separate --

10 DR. SUL: I think that's the letter of the law
11 again. First it's the spirit of --

12 DR. HONG: It's the letter of the spirit of
13 the law.

14 DR. SUL: Right.

15 MR. KARST: If the law allows it, it'll
16 happen, so.

17 DR. SUL: Yeah.

18 DR. LEWIS: Did you -- were you leaning
19 forward there? Could you say that again?

20 MR. KARST: Oh. Sorry. I said if the law
21 allows it, it will happen, so.

22 DR. SUL: Exactly.

1 DR. KUMMAR: So I guess the question I had is
2 that if they're doing a biomarker X tissue agnostic
3 trial and then they come in -- I mean it's fine that, I
4 know, I don't feel strongly about penalizing them just
5 because they came earlier with pancreatic cancer and
6 changed their plan. But then we have to make sure that
7 the biomarker X clinical trial had enough number of
8 pancreatic cancer patients with biomarker X positive to
9 say that stand alone it wouldn't need approval for
10 pancreatic cancer, right?

11 Because I mean not all -- once you have these
12 multi-histology, it could be ten histologies, but you
13 come with the eleventh, presuming that it's also
14 biomarker X positive. So then how many, how do you
15 independently power to say now you want to get a
16 pancreatic cancer approval? So should it have X number
17 and show positivity to do that? Because I don't think
18 you can just extrapolate.

19 DR. LEMERY: I, I think we're talking about
20 potential situations where a drug has multiple pathways
21 of, of action. You know, it, it's not just through
22 MSI. It's the mutation burdens through, you know, we

1 don't really know the -- I mean if you have a clean, if
2 you have a clean TKI that's, you know, it may be less
3 of an issue, but if you have a, maybe if you have a
4 dirty TKI that affects multiple pathways you can see a
5 scenario -- I mean it's not likely, but it's possible
6 if you have --

7 DR. KUMMAR: I don't know, but I'm saying if
8 we, if the approval is for pancreatic cancer, is there
9 enough evidence to support pancreatic cancer stand-
10 alone approval? Or have enough patients with
11 pancreatic cancer that are biomarker X positive being
12 treated and shown to derive benefit?

13 DR. LEMERY: Well, I think for -- to get an
14 approval on pancreatic cancer you'd have to show that
15 the drug is safe and effective in patients with
16 pancreatic cancer.

17 DR. KUMMAR: Yeah. That's what I mean. I
18 mean you can't take the biomarker X --

19 DR. LEMERY: Right.

20 DR. KUMMAR: -- tissue agnostic where you have
21 your three, four patients of each histology, small
22 study, to kind of do it, right?

1 DR. LEMERY: Well, right, but I think we're
2 talking about -- the, the pancreatic cancer circle here
3 is talking about both patients who are biomarker
4 positive and negative. So you would have --

5 DR. MOSCICKI: Yeah, but your -- it's very
6 confusing 'cause you're talking about exclusivity for
7 the biomarker X positive.

8 DR. KUMMAR: Biomarker X positive.

9 DR. MOSCICKI: And, and, you know, so now
10 you've sort of redefined it. It's no longer just
11 histologically based pancreatic carcinoma. Now you've
12 redefined it by the biomarker presence, which now makes
13 it belong to the blue subset. That's why we're here.

14 DR. SUL: So I, I don't know that's it's
15 really redefining as much as it is we're going to pluck
16 these patients out of the -- the original approval is
17 for a tissue agnostic indication, biomarker positive.
18 However, because you already previously had designation
19 for pancreatic cancer, you could have had it for
20 gastric or whatever, whatever other smaller subsets.

21 We're just going to pluck out that -- we're
22 carving out that group to provide you with exclusivity.

1 It's not saying anything about, you know, the, the
2 approval and activity in that.

3 DR. LEMERY: Yeah, but -- so I mean just take
4 the -- I, I mean you could -- here you could think of
5 PD-1. So MSI, all indications above 200,000, and then,
6 you know, whatever Merck, BMS, any of the companies
7 come in with, you know, an, an indication solely in
8 neuroendocrine tumors or bladder cancer, you know. How
9 do we deal with that here? Should -- do you, how do
10 you assess the MSI population who has both
11 neuroendocrine or bladder cancer in, in those scenarios
12 and I think that's their question.

13 DR. LEWIS: Okay.

14 DR. MOSCICKI: Yeah, but that's part of the
15 convolutions here, is sort of putting in after the
16 fact, you know, the plucking out as opposed to the fact
17 that they early on had an orphan drug designation for
18 all pancreatic cancer, assuming the clinical trials
19 showed an, a, an efficacious benefit in undefined
20 pancreatic carcinoma based solely on the histology.

21 Then to retrospectively pluck out the
22 biomarker X doesn't seem right according to the

1 original principle that I was trying to say. Then,
2 then in fact, that is a different disease and still
3 deserves.

4 Now if instead, you know, the sponsor sought
5 to get biomarker X positive pancreatic carcinoma,
6 conducted the, based on this and didn't have evidence
7 that biomarker negativity contributed to the benefit,
8 you know, that's a very different scenario. So like
9 I've often heard in these buildings, it depends.

10 DR. LEWIS: Thank you. Due to time I'm going
11 to be sure that we -- oh, I, I think we had -- maybe
12 this one just was -- so I think that may wrap up our,
13 our, our topic questions.

14 There are some that came from outside in the
15 webcast. Are there also anybody who has a, a question
16 from in the room? Do you want to, do you want to start
17 at the bottom one?

18 Okay. Let's start at the top.

19
20 Oh, okay. I'm going to go. We have from our second
21
22 discussion a situation where Company A seeks an

1 indication for a specific tumor type and it's, they're
2 saying ALK in non-small cell lung cancer and they
3 gained exclusivity for this orphan population, all
4 right?

5 So, Company A indication for a specific tumor
6 type and gains exclusivity for this. How would FDA
7 handle the approval of the same drug for a tissue
8 agnostic indication in the future? Would the
9 exclusivity for ALK non-small cell lung cancer
10 preclude Company B from gaining a tissue agnostic
11 indication for all cancers expressing ALK positive
12 until Company A's exclusivity expired?

13 And with this situation, what would be the
14 situation where Company B would get a carve out in
15 their label excluding the protected subset?

16 DR. STARTZMAN: From the discussion that we've
17 heard today, it sounds like we would consider tissue
18 agnostic to be a different, you know, disease or
19 condition or indication from the more tumor specific.
20 It would be just the ALK positive non-small cell lung
21 cancer, and therefore the exclusivity would not carve
22 out that from the, from the tissue agnostic approval.

1 DR. LEMERY: So I guess, so in this scenario
2 you would have, just to simplify, you have ALK positive
3 lung cancer gets approved, it has a certain
4 exclusivity. It may have orphan designation, the
5 tissue agnostic has orphan designation. It gets
6 approved three years later. Once the exclusivity runs
7 out for lung then a, a generic company could market
8 their product for ALK positive lung cancer, but they
9 couldn't include the ALK positive tissue agnostic in
10 their label until the exclusivity runs out for the
11 tissue agnostic.

12 DR. HONG: But I, you know, there's, there's a
13 similar -- I mean entrectinib, for example, targets
14 both ALK and NTRK, right? So, I could see a situation
15 where they've applied for or let, let, let's say they
16 get exclusivity for ALK positive cancer, but then they
17 apply for a designation or they get exclusivity for
18 tumor agnostic in NTRK in the future or something like
19 that. I could, I could totally see that being a
20 conceivable, reasonable pathway.

21 DR. LEWIS: Mm-hm.

22 MR. KARST: Yeah. It, it, it, if you, if you

1 view it in the light of, if you almost rename them.
2 Say, you know, indication X is multiple myeloma and
3 indication Y is leprosy. Okay, two very different
4 indications and, and if we view these as that way it
5 actually becomes very easy. Carve out one or they both
6 get their own periods of exclusivity if they're both
7 designatable, and once one period ends it, it's
8 no longer protected, then generic can come in and get
9 approval for leprosy while the multiple myeloma
10 indication is protected, for example.

11 DR. SUL: So it sounds like what you and I
12 think many others on the panel have proposed is really
13 to think of them as almost completely unrelated
14 diseases, which I think is very difficult given what we
15 know about the, the science and why we're having this
16 discussion.

17 MR. KARST: Right.

18 DR. SUL: Yeah.

19 MR. KARST: I think, and not being a
20 physician, but, but, yeah, mentally I think it is
21 difficult to separate them because they are so close to
22 one another, but if, if the paradigm here, again, is

1 that they are different diseases, then they are, in
2 fact, different diseases as different from, you know,
3 multiple myeloma and, and leprosy, right?

4 Now what it's going to come down to, though,
5 of course, is how the labeling is going to be written
6 for these products and how you describe a tissue
7 agnostic product, you know, the biomarker versus one
8 that's organ specific, right? So the, the devil will
9 always be in the details particularly when it comes to
10 labeling carve outs and generic approvals, but --

11 DR. MOSCICKI: I, but I would agree that data
12 will always matter.

13 MR. KARST: Yeah.

14 DR. MOSCICKI: Right? In the end it will
15 matter, but, you know, I, I, I think to some degree it,
16 it doesn't help to confuse in a way the science with
17 the policy because, you know, we, you have, you're
18 having this discussion partly because the scenarios
19 seem awfully convoluted in so many ways, right? And so
20 many different ways to think about them.

21 So I think the principle that we were
22 advancing is to simplify this by making a policy, not

1 changing science, not trying to, but, but treating this
2 in a policy manner by saying, by establishing this
3 policy you get clarity. And, and it's much easier to
4 work and make those decisions that you need to make.

5 DR. SUL: I think -- and that's, that's
6 definitely true when you, when you sort of start out
7 with a, with a standing principle that then you kind of
8 refer back to when you're making decisions. But I
9 think part of the concern that the, the Office of
10 Orphan Products has had is what are the, ultimately the
11 implications later on down the line.

12 Because, you know, we're not just talking
13 about designation for designation's sake. We're
14 talking about the incentives and the exclusivity that
15 comes with it and the potential to block, you know,
16 access to, to other drugs.

17 DR. LEWIS: I think, I think it's true that,
18 that certainly a policy that simplifies things is
19 appealing and it's something that has been discussed as
20 a way to help us through some of these scenarios. But
21 I do think the consideration of the implications is
22 something that we'll be thinking about as we take in

1 all of this great input we've received today. And as
2 we're going forward on a guidance document, looking at
3 what are those implications.

4 Certainly, I do appreciate simplicity. That's
5 a great, that's a great opportunity, but we want to
6 ensure that we get this balance right between giving
7 the incentives and protecting the intent of the Orphan
8 Drug Act, ensuring that we are doing the right thing
9 for these people who are actually having these
10 conditions.

11 And so a lot of complexity. Some of the
12 questions we've received, people trying to understand a
13 little bit about the testing aspects and are we going
14 to be looking at responses and changing our decisions
15 based on responses. Are we going to -- somebody even
16 was looking back for clarity on questions about will we
17 designate multiple products for the same, multiple same
18 drugs for the same condition up until that approval.
19 And, yes, we will.

20 So people are, are going to be struggling with
21 some of the inputs and the implications of what's been
22 said, but I do think we're coming close to the end of

1 our time and I just want to give an opportunity for our
2 panelists to, to say if you have a particular final
3 thought as we just come across.

4 I'm going to start down on the other end. We
5 started with introductions down with Kurt. Pam, do you
6 have anything as we come across down here that we want
7 to just say as closing thoughts?

8 CLOSING REMARKS

9 MS. GAVIN: Thank you. Just to -- a couple of
10 really quick thoughts and maybe reinforcing some of
11 them that were made earlier. I think providing as much
12 data to OOPD as possible to help understand the context
13 and as best you can because you can't predict the
14 future is important.

15 And I think also to remember that these are
16 patients that we're dealing with here and it's hard
17 just following the conversation. And when we talk
18 about the science to recognize that what does that mean
19 for patients. As a patient can I be in both the red,
20 the red circle and the blue box? It doesn't seem
21 logical.

22 So we've got to think through these processes,

1 as well as what does the implementation look like from
2 a sociopsychological and socioeconomic perspective
3 because it, it runs all the way through to the end to
4 access.

5 DR. LEWIS: Thank you.

6 DR. RUBIN: So I guess I'll sort of echo that.
7 I think both the tissue agnostic approval and pathway
8 and, and orphan drug designation, they're both good for
9 patients. And I think although there are complexities
10 that come into play with having both around, they're
11 not opposing, and I think that it was a good discussion
12 today. And I think, I think it can be worked through
13 in individual situations to, to preserve the intent of
14 both.

15 DR. MOSCICKI: Yeah, I would echo that and I,
16 I, I believe that the Agency deserves good recognition
17 for bringing this topic and discussion forward. I
18 think for its forward-thinking on tissue agnostic
19 indications and it's willingness to take on the
20 complexities that that innovation has engendered.

21 And, you know, I think that I've already had
22 my say about simplicity and the virtues of that. And

1 I, I, I also want to come back to while affordability
2 is important, there's no question about it for
3 patients, we still have 7,000 rare diseases and only
4 500 approvals. Although that's great that we have 500,
5 but largely thanks to the Orphan Drug Act.

6 So those incentives remain important and I'll
7 leave it with that.

8 DR. LEMERY: Nothing, nothing else to add.
9 Just, you know, thank everyone for coming and giving
10 their, their input.

11 DR. KUMMAR: Yeah. Thank you for having me on
12 the panel. It's been a very interesting discussion.
13 My only two cents, simplicity and then sort of
14 encouraging is all great, but here we're not talking
15 about two diseases. It's, part of the biomarker
16 disease is actually part of a bigger whole.

17 So, I think it's not as simple as pluck it out
18 or let's treat them as leprosy versus myeloma. This is
19 a subset of a bigger whole. And so I think each has to
20 be reviewed very carefully in the context of the larger
21 knowledge base and what the exclusivity, as well as the
22 approval would have an impact on which patient gets

1 treated which way.

2 So, I think it has to be thought through each
3 case individually.

4 DR. HONG: Yeah. I, I, I echo the same
5 thoughts as Shivaani. I think this is a complex issue,
6 but I, I, I applaud the FDA for, for doing this because
7 I know, you know, for many of my patients it's, it's,
8 it's, it's really, I think, big hope. And I, and, and
9 I think going back to my, my last comment, I think
10 oncologists are behind you guys. We're still trying to catch up
11 in some sense to the science and to the regulation.

12 DR. SUL: I just want to thank everybody and,
13 and for their input and for, for participating and
14 spending the day talking about this complicated topic.
15 And I did spend some time in the Office of Orphan
16 Products and my head would spin sometimes trying to
17 wrap myself around some of these issues.

18 And it's a very different way of thinking from
19 being on the Review Division. And so, you know, I
20 really appreciate, you know, what the Office is up
21 against, especially with this new science.

22 And one thing I will say is that, you know,

1 whenever I was struggling with something I would always
2 try and come back to what the original intent of the
3 Orphan Drug Act is and, and, you know, actually printed
4 it out and, and pasted it on my desktop just to remind
5 me, okay, this is really what we need to focus on. And
6 so it, really whatever we can do to, to keep the
7 incentives there for developing these products is
8 important.

9 DR. LEWIS: Thank you.

10 DR. STARTZMAN: I just want to thank
11 everybody. I think the discussion has been, has
12 developed good guidance for how we can deal with this
13 evolving science. And thank you.

14 DR. MELLIS: I'd like to echo the, the
15 comments of my previous, previous panelists who spoke
16 and thank everyone and thank the Agency in particular
17 for this truly visionary science-based initiative.
18 And, and I'm confident that the complexities can be
19 worked through and that we can really work together to
20 bring forward new medicines for patients in need.

21 DR. LE: Yeah. I just wanted to say that
22 encouraging a tissue agnostic approach actually is a

1 way to provide access to patients with orphan diseases
2 'cause they aren't really included in a lot of the
3 other studies.

4 DR. STEWART: I think I mostly will echo what
5 other people have said, but first thanks to the FDA for
6 providing a platform to discuss this important issue
7 that truly does give access to patients to innovative
8 therapies. And recognizing that, that tissue agnostic
9 drug approvals and drug development is really changing
10 the landscape. And recognizing that policy needs to be
11 able to capture that.

12 So I think moving forward it's, it will be
13 critical to really think about how we are going to
14 define diseases and whether every biomarker that may
15 exist across tumor types truly rises maybe to the level
16 of being defined as, as a disease or simply just a
17 biomarker that, that exists.

18 And in addition I was, I'm glad CDRH was
19 here and I hope there's additional opportunity to
20 discuss the important role that the diagnostic plays in
21 this conversation. And particularly when it comes to
22 making sure patients do or don't receive a drug that's

1 been approved based off of a, a, of a biomarker.

2 MS. SHER: Again, just echoing our thanks to
3 FDA for holding this meeting. I think it's a
4 reflection of FDA's long tradition of ensuring that
5 we're really looking closely at the need for innovation
6 on the one hand and competition at the end of the
7 appropriate exclusivity periods. We share that
8 commitment and really appreciate this Commissioner's
9 and this FDA's focus on the importance of access to
10 generics and biosimilars. So, we really appreciate
11 being able to be a part of this today. Thank you.

12 MR. KARST: And I echo those comments as well
13 and I think, you know, throughout the history of the
14 Orphan Drug Act we've -- Orphan Drugs has constantly
15 been faced with the new technology and science and it
16 creates new issues. But at the end of the day, you
17 know, whether we're talking about fusion proteins or
18 gene therapy, sameness issues, there's always that
19 elegant simple issue or resolution and there's a very
20 complex one.

21 And I think we have that here as well and,
22 and, and, and I would hope that the Office ends up

1 writing guidance and following, following that pattern
2 of adopting the very clear-cut, black and white, easiest
3 way to implement the act.

4 DR. LEWIS: So thank you, all our panelists.
5 I don't know, Donna, if you want to make any final
6 comments from a testing aspect?

7 DR. ROSCOE: Yeah, actually I would just like
8 to say one thing and that's that as you're developing
9 policy, it's very important to have the definitions in
10 place and the -- because the definitions really enable
11 you to move that policy forward. And I think perhaps
12 in this setting part of that of establishing
13 definitions is appreciating the uncertainty around
14 those definitions and identifying.

15 Because when you talk about a biomarker, a
16 disease defined by a biomarker, you need to understand
17 is the biomarker driving the disease or is it just an
18 outcome of the disease, because now you really aren't
19 defining disease if it's the latter.

20 So, understanding the uncertainty around those
21 definitions and then perhaps provocatively thinking
22 about ways to incorporate that uncertainty into the

1 clinical trial designs so that you can move forward the
2 orphan product while maintaining an understanding of
3 the science that's coming out of it.

4 DR. LEWIS: Thank you. I want to thank all of
5 our panel today. You've come from many different
6 perspectives and given us a lot to think about, whether
7 it's approaching simplicity, whether it's thinking in
8 more specific definitions, lots of input that we
9 appreciate.

10 It is an exciting time. We're not just at
11 500. We're almost at 700 approvals now. And the
12 people who carry this out in the Office of Orphan
13 Products Development, I just treasure you. You're,
14 you're fantastic. So, thank you so much for all the
15 preparation.

16 Our, our logistics folks, I can't say enough
17 about Joohee. I, I just lost sleep wondering, you know,
18 I hope you're okay. Get here safely today. So I think
19 that all of you who've provided your comments today we,
20 we appreciate it.

21 There is still an opportunity to provide
22 comments. We have a docket that's open until early

1 June. So please do submit your, your thoughts, your
2 input.

3 I want to also thank Nina Hunter who's been
4 terrific support from us from OMPT. Oh, there's our
5 panelists who've just shown up again. But these are
6 tough questions. We do, you're right, focus a lot
7 about these scenarios and making sure we do this right,
8 and your input is just so critical to us.

9 Everyone made a great sacrifice to be with us
10 today. Nicole Wolanski, thank you for your fabulous
11 support as well. That whole group. Christine, thank
12 you. Dev, thank you. Chip, thank you for being
13 up here.

14 And if there's any other final comments, raise
15 your hand right now. Otherwise -- oh, there is one. I
16 see one in the back. Here you go.

17 [Uros Djekic (Shire)]: It's, it's -- and I'm sorry for
18 --

19 DR. LEWIS: No. That's good. That's good.

20 [Uros Djekic (Shire)]: -- for, I guess, asking the
21 question late, but I guess given obviously the title
22 and the focus on oncology products --

1 DR. LEWIS: Mm-hm.

2 [Uros Djekic (Shire)]: -- and the implications for the
3 guidance document that is going to be applicable, I
4 guess could you comment to the extent possible how this
5 discussion and information and topics would apply to
6 non-oncology designations? And will there be maybe two
7 separate guidance documents or to, to the extent
8 possible?

9 DR. LEWIS: All right. Thank you for the
10 question. Yes. We have focused today on oncology and
11 acknowledging full well that this is not a, a set aside
12 by itself, that, that the many important advances
13 outside of oncology are critical to rare disease issues
14 in general.

15 So will there be two guidances? Right now
16 we'll focus originally on this oncology. Where we see
17 principles that are generalized, we will, we will
18 certainly try to include that. We'll try to think
19 about what we've heard today. And in the future we, of
20 course, want to, to be able to make use of that
21 guidance, whether -- I can't really speak about how
22 soon.

1 One of the things that is, that we started
2 here is because we had some experience and it helps the
3 Agency to get a little bit of experience with
4 something. And as we get a little more experience
5 outside oncology, that's where those principles might
6 show themselves to be simple and able to be applied
7 simply, or they may even turn out to be a little bit
8 different.

9 For example, it's not always tissue agnostic,
10 but agnostic in a sort of an analogous way. If you
11 look at our ophthalmology, it's right there in the
12 retina, but it's still grouping different conditions
13 into one setting. So, we've been saying tissue
14 agnostic, but in our minds we're thinking like you are,
15 how does this apply to other agnostic situations that
16 we'll be encountering.

17 I know there's more work coming up in the near
18 future looking at these types of issues. So, I thank
19 you for your question. It just drives us more and I
20 know Christine's always asking me on this question. So
21 we, we hear you and respect that need for the future.

22 So with that, nothing else? All of you, thank

1 you so much for joining us and for those who made this

2

3 possible, my appreciation. Everyone take care and I

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5 hope you have safe trip back. Thanks so much.

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CERTIFICATE OF NOTARY PUBLIC

I, KeVon Congo, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



KeVon Congo

Notary Public in and for the

State of Maryland

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CERTIFICATE OF TRANSCRIBER

I, Penny Knight, do hereby certify that this transcript was prepared from audio to the best of my ability.

I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of this action.



May 17, 2018

Date

Penny Knight

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