U.S. FOOD & DRUG ADMINISTRATION

Regulatory Framework

Approval Pathways and Endpoints in Primary Sclerosing Cholangitis

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PSC Forum
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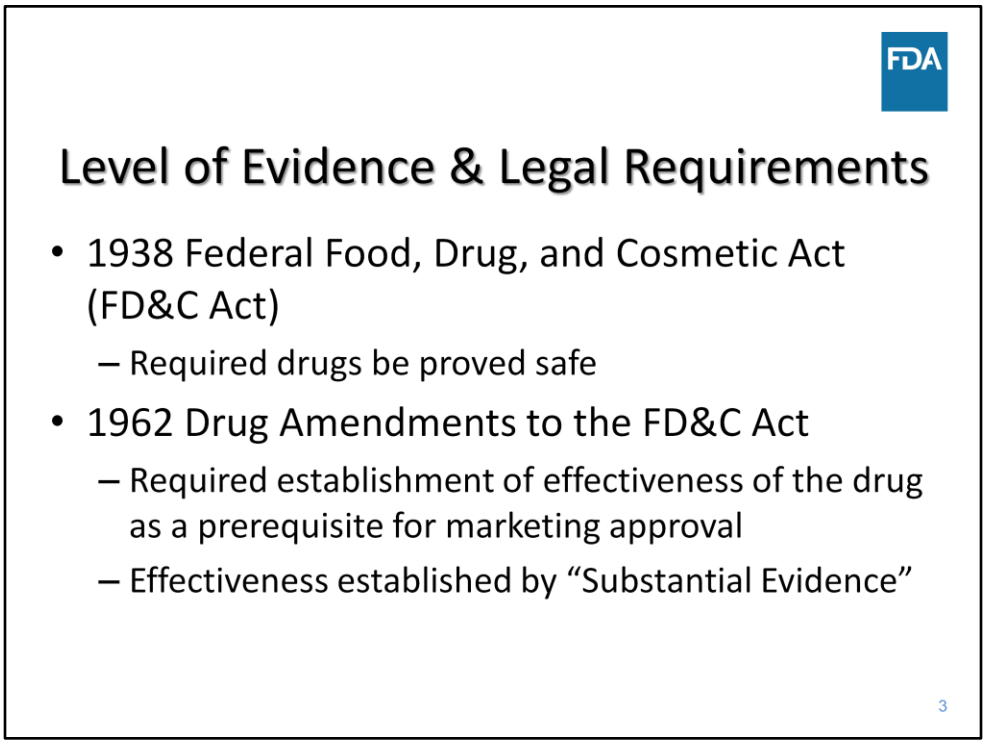
Disclaimer

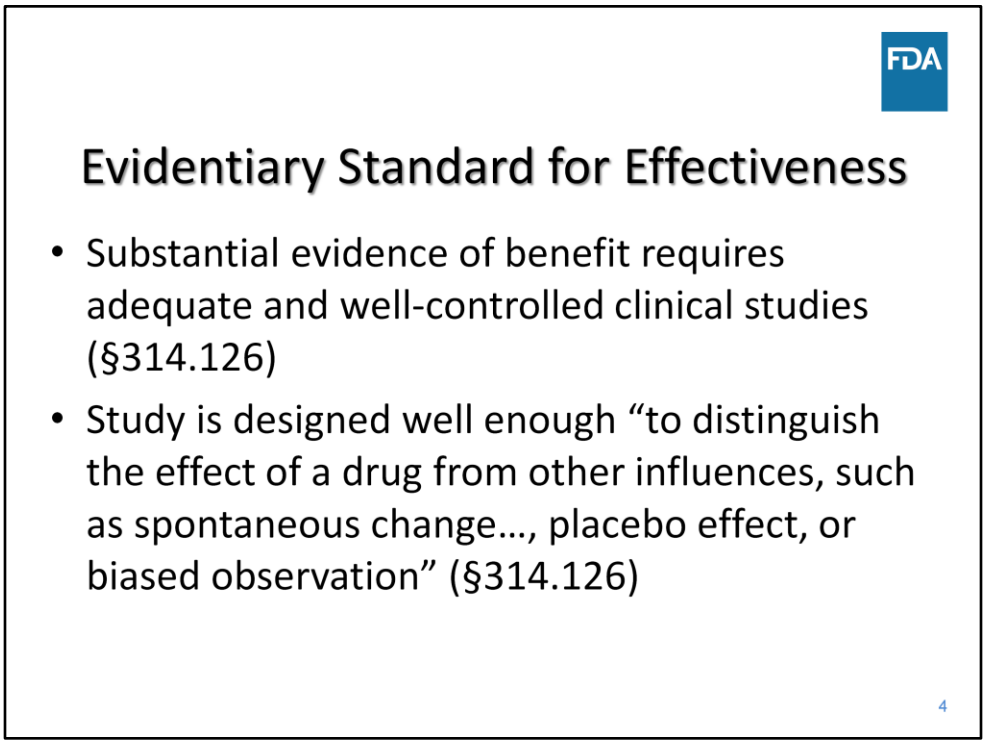
- The views and opinions expressed here are my own and do not represent official guidance from the FDA
- I have nothing to disclose



The federal food drug and cosmetic Act was originally passed in 1938 and required drugs be proved safe. (click)

In 1962, Congress amended the FD&C Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies.

Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product for use.



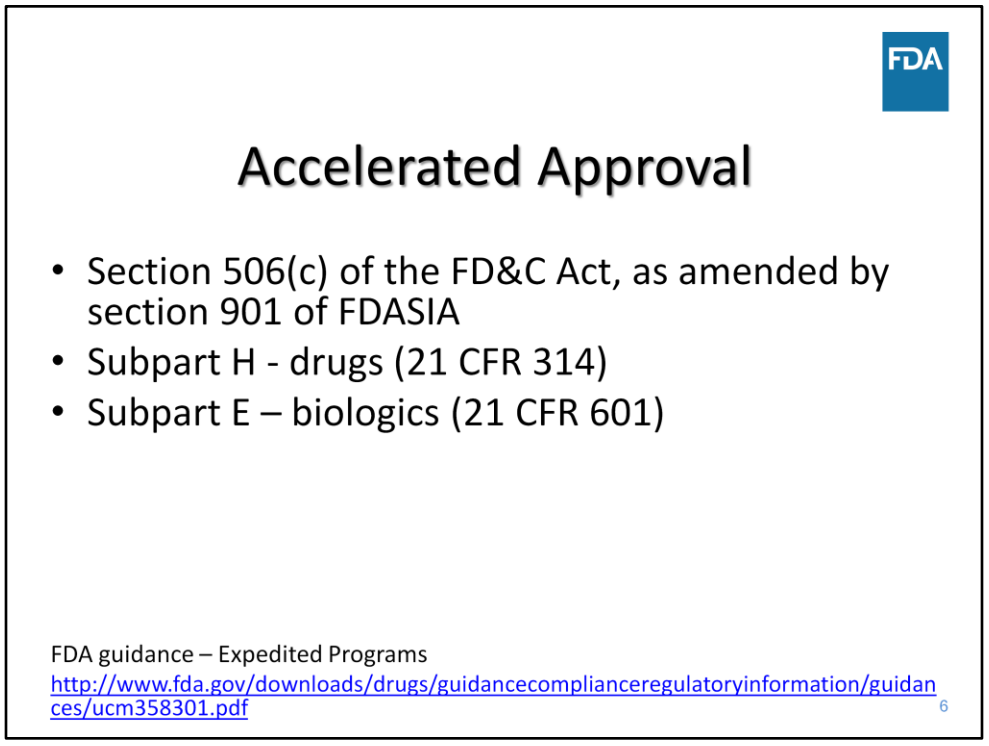
Section 505(d) of this law defines "substantial evidence".

It has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing.

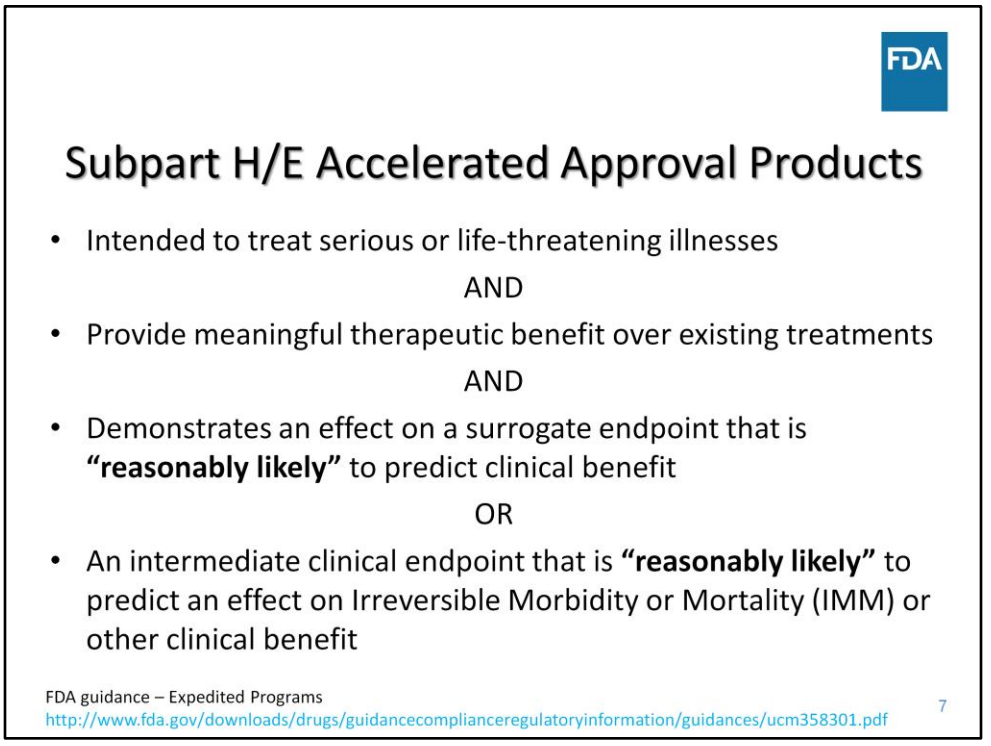
There are 2 approval pathways.

We will focus our discussion on the **accelerated approval pathway** and how it relates to development program for PSC.



Because of the need to obtain and approve drugs for life threatening diseases (such as HIV), in 1992 FDA promoted rulemaking that defines approval based on endpoints that measure a surrogate that is reasonably likely to predict clinical benefit, or a clinical endpoint other than survival or irreversible morbidity or mortality.

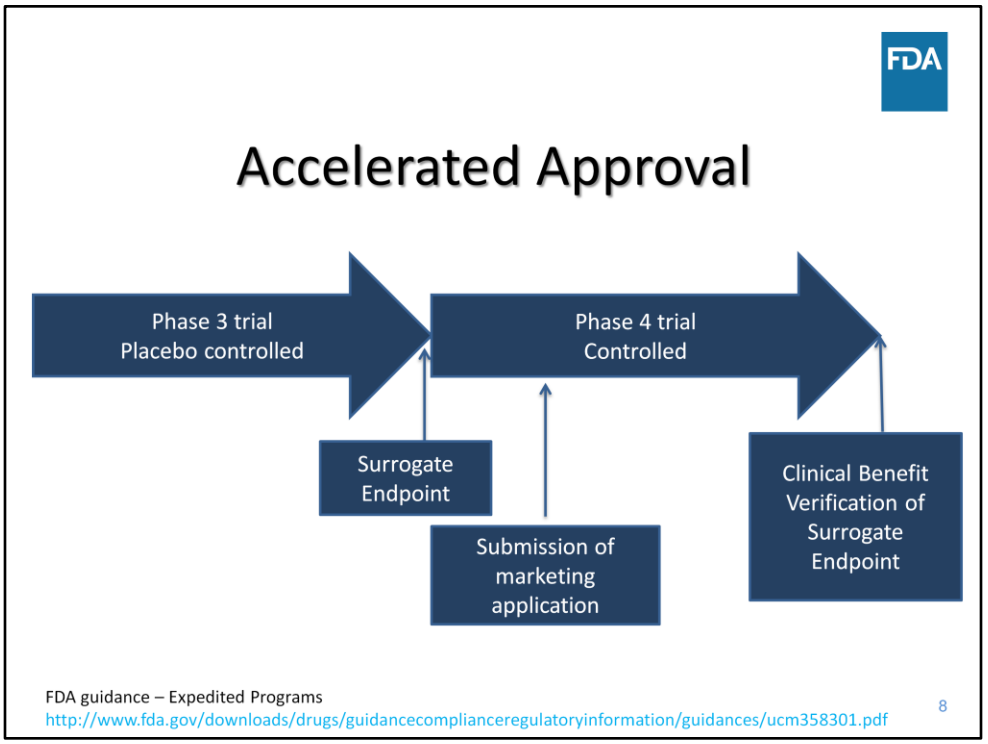
THE REGULATIONS that address marketing under accelerated approval ARE CODIFIED IN 21 CFR part 314 – subpart H for drugs and 21 CFR part 601 – subpart E for biologics



The Guidance states that the accelerated approval candidate product must be intended to treat a serious and life threatening illness, and provide meaningful therapeutic benefit compared to existing treatment.
Approval based on a surrogate endpoint needs to be based on adequate and well-controlled studies.

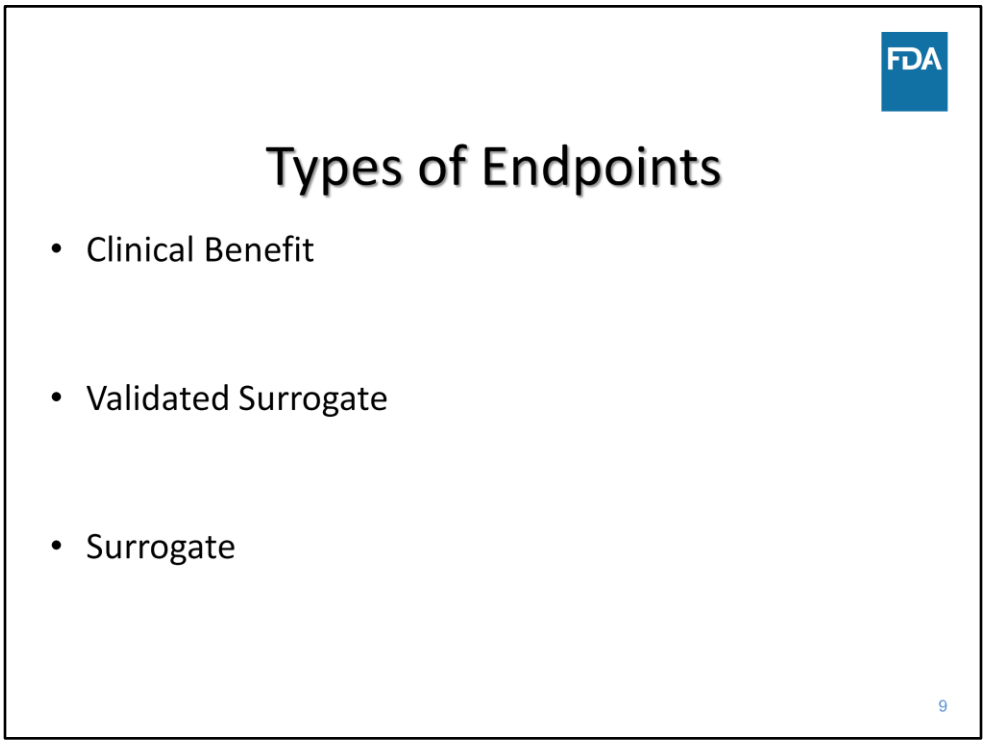
Therefore the standards for the data and clinical trials required for accelerated approval are the SAME as for regular or traditional approval,
the only difference is in the type of endpoints [click] such as the use of surrogate endpoint or [click] of the use of clinical endpoints other than irreversible morbidity or mortality.

The term "reasonably likely" implies that some uncertainty remains about the relationship of the surrogate to the clinical benefit to the patient. Therefore, accelerated approval is contingent on a sponsor's agreement to conduct additional post-approval (phase 4) studies to verify and describe the drug's clinical benefit.

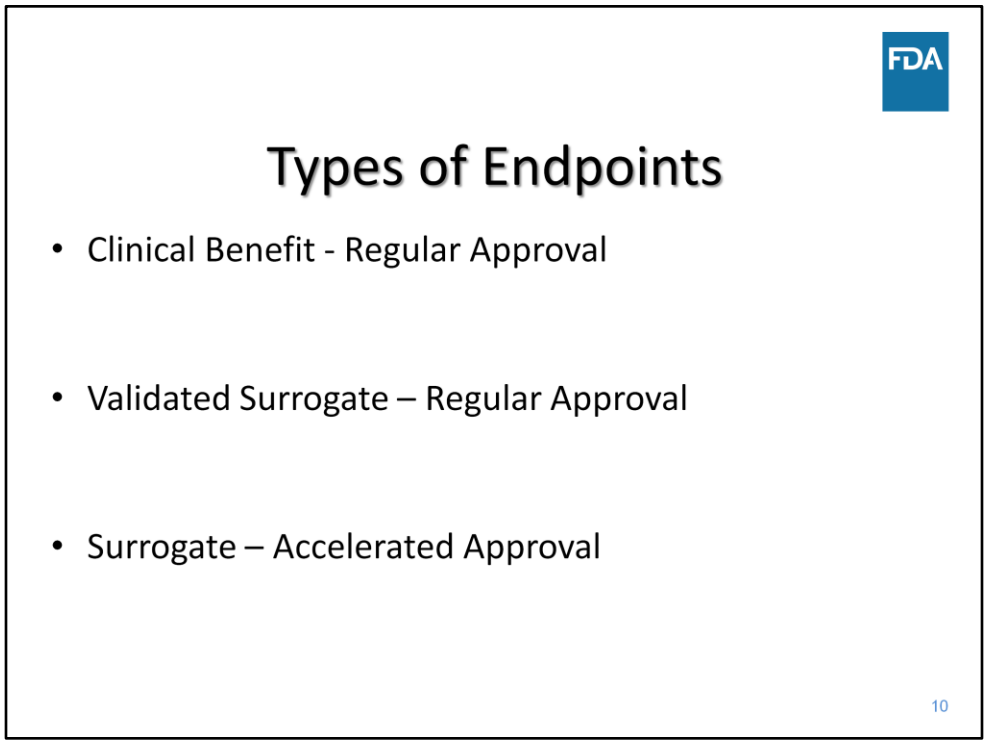


Again, Accelerated approval has the same requirement as a regular approval. Because of the use of **surrogate endpoint**, [click] AA pathway generally requires that a phase 4 trial be underway at the time of [click] **marketing approval** to verify and describe the [click] **clinical benefit**.

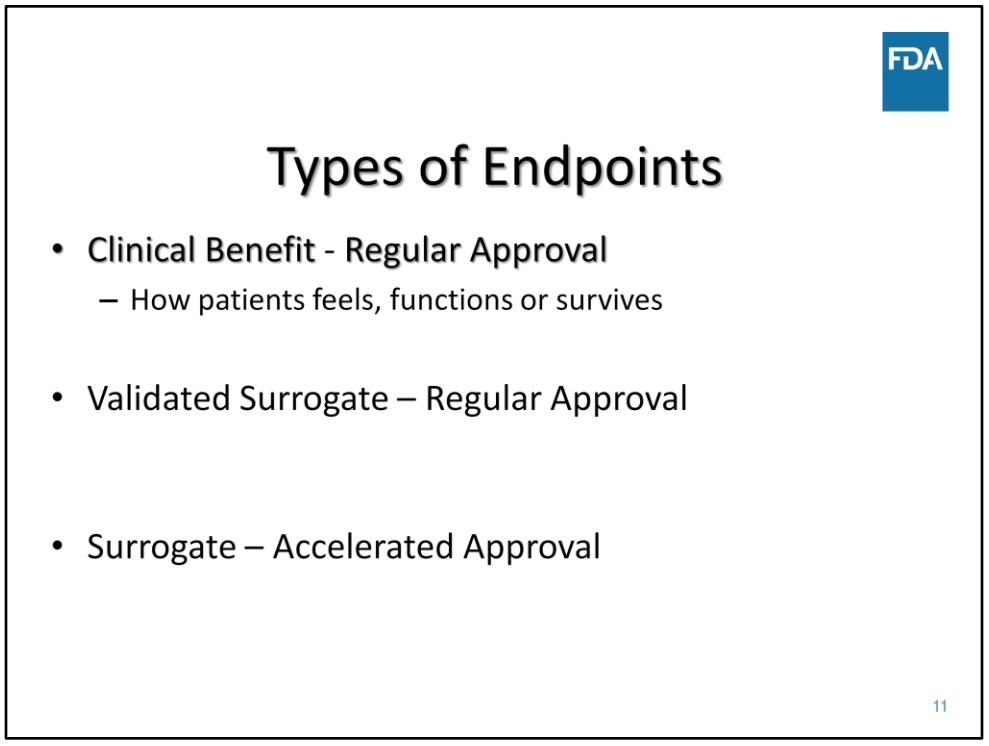
It is important to note that accelerated approval on a surrogate biomarker is NOT a consolation prize for failed clinical trials powered to detect a difference in a clinically meaningful endpoint.



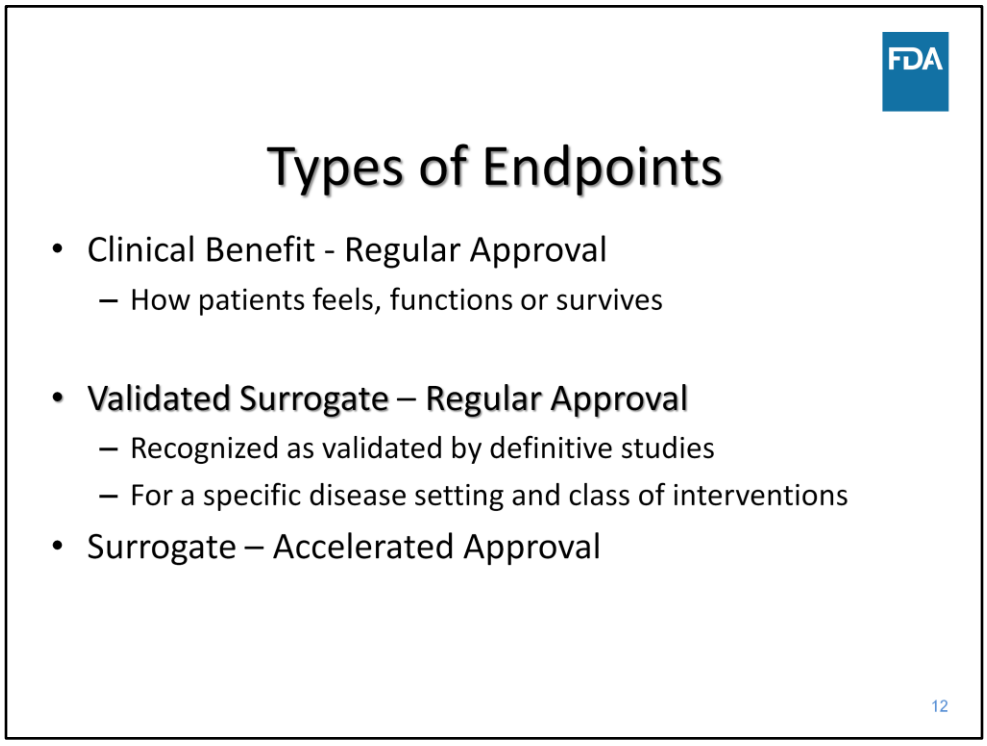
So again, just to hone in on the acceptable endpoints, there are 3 different types of endpoints:
Clinical benefit, validated surrogate and a surrogate endpoint.



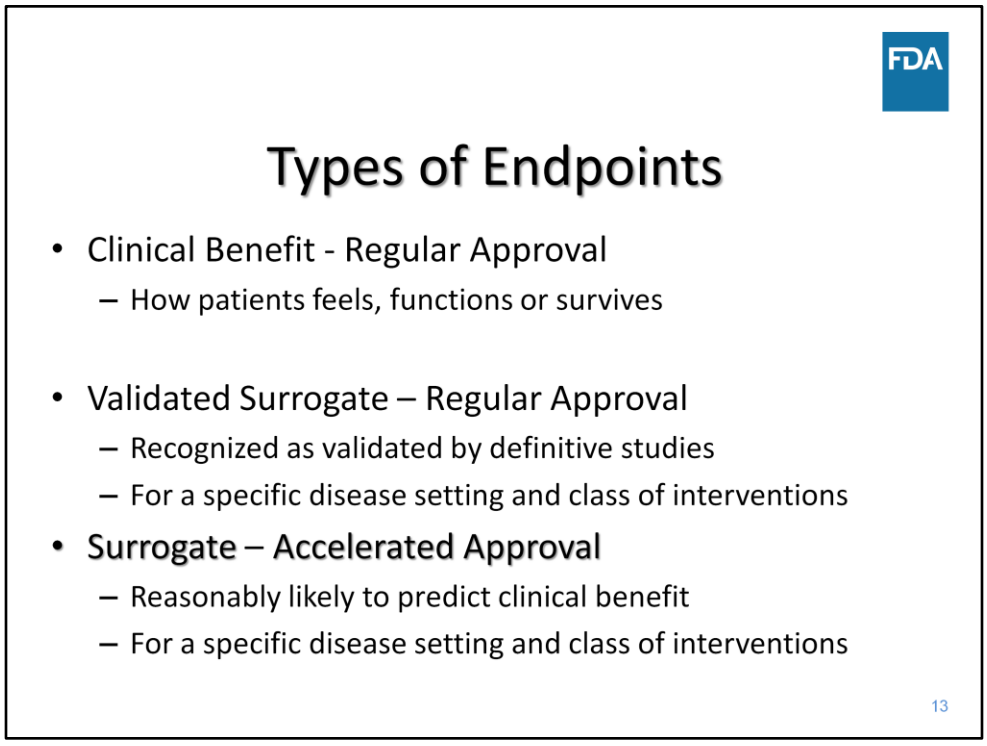
Clinical benefit and validated surrogate endpoints are used for regular TRADITIONAL approval.
WHEREAS a yet-to-be-validated surrogate but resonably likely to predict clinical benefit can be used for accelerated approval.



As you know, given the legislative background, marketing approval for a product requires that a product be safe and effective with proof of clinical benefit, as in how patients feels, functions or survives.

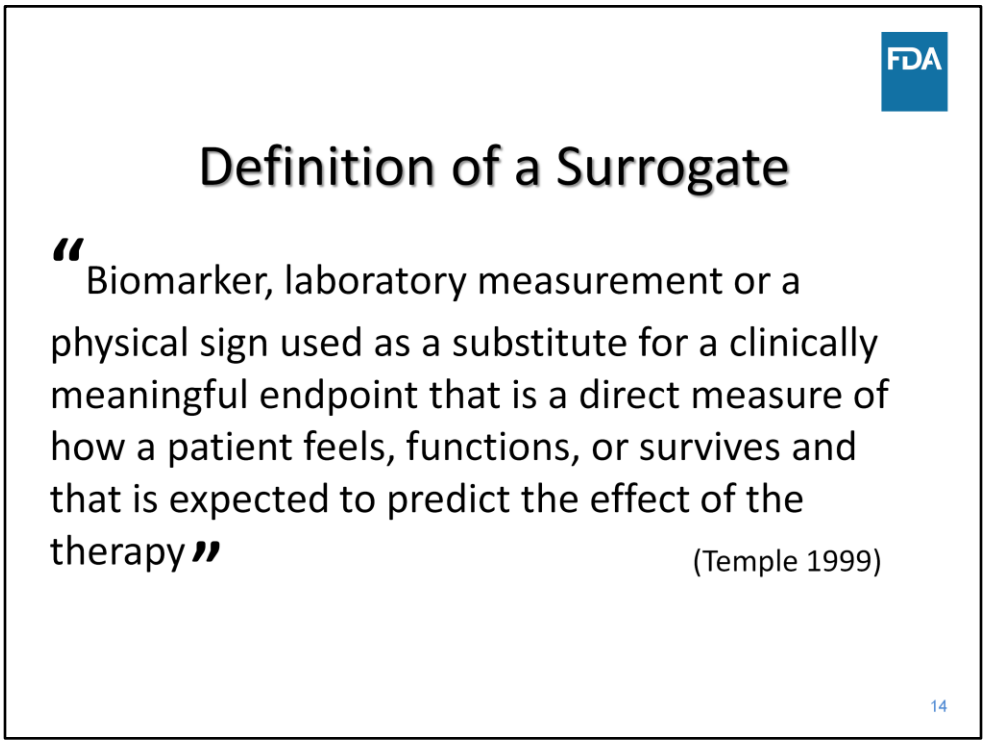


In order for a surrogate to be validated, or ready-for-regulatory-use, it requires rigorous evaluation. It has to prove that it can predict clinical benefit time and time again in an independent population to be considered "validated".
An example would be the clearance of bacteria from the bloodstream as evidenced by a lab measurement of bacteria in the blood or hemoglobin A1C in Diabetes.

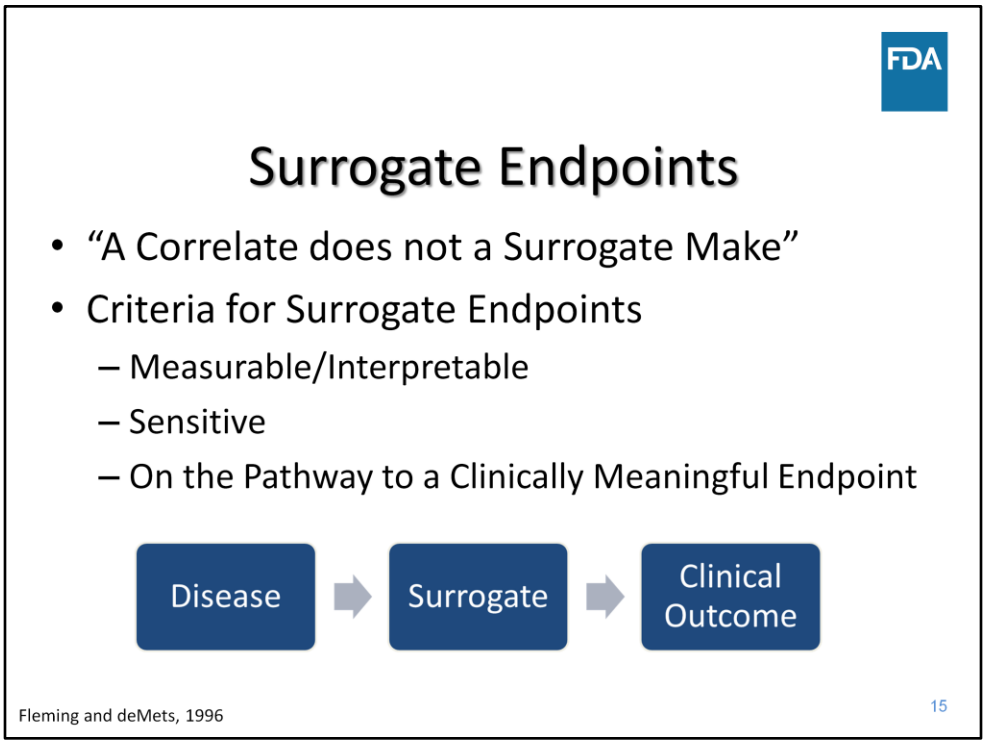


a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit could be used for accelerated approval.

Having said this…
If there is insufficient evidence to support reliance on the marker as either kind of surrogate endpoints (i.e validated or not validated) , then the marker cannot be used to support traditional or accelerated approval of a marketing application.
The level of evidence necessary to determine whether a surrogate is validated (i.e., acceptable for traditional or regular approval pathways), or if a surrogate is reasonably likely to predict clinical benefit, is made on **a case-by-case basis** by the Agency.

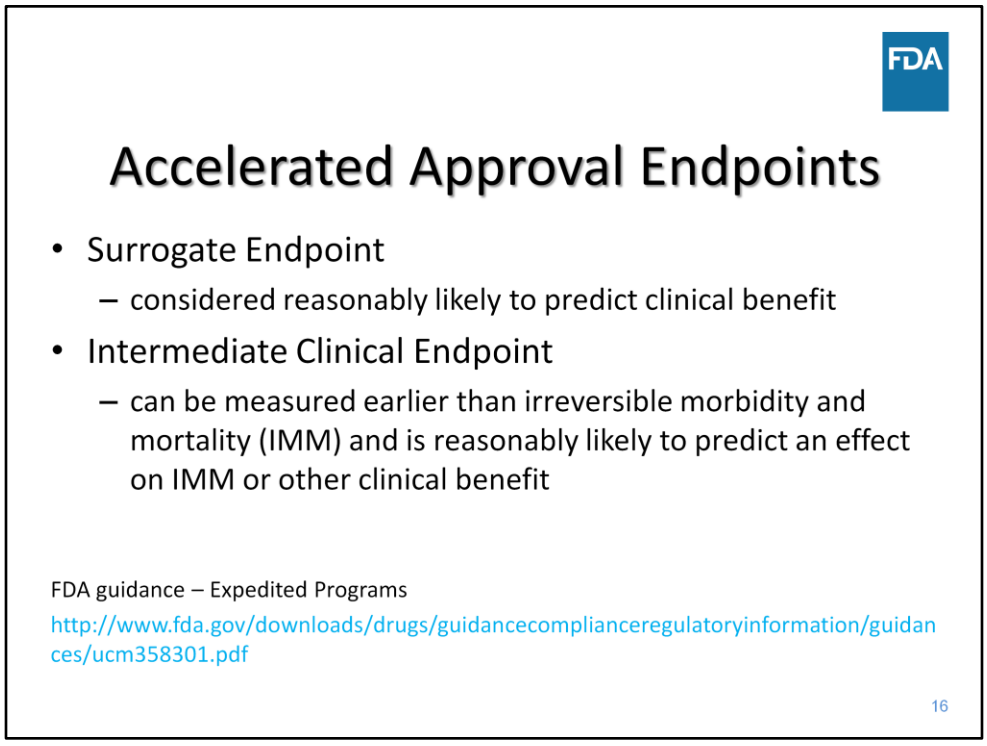


Before we go any further, we need to define what a surrogate is.
It is a biomarker, laboratory measurement, or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives, and predicts the ultimate clinical outcome.



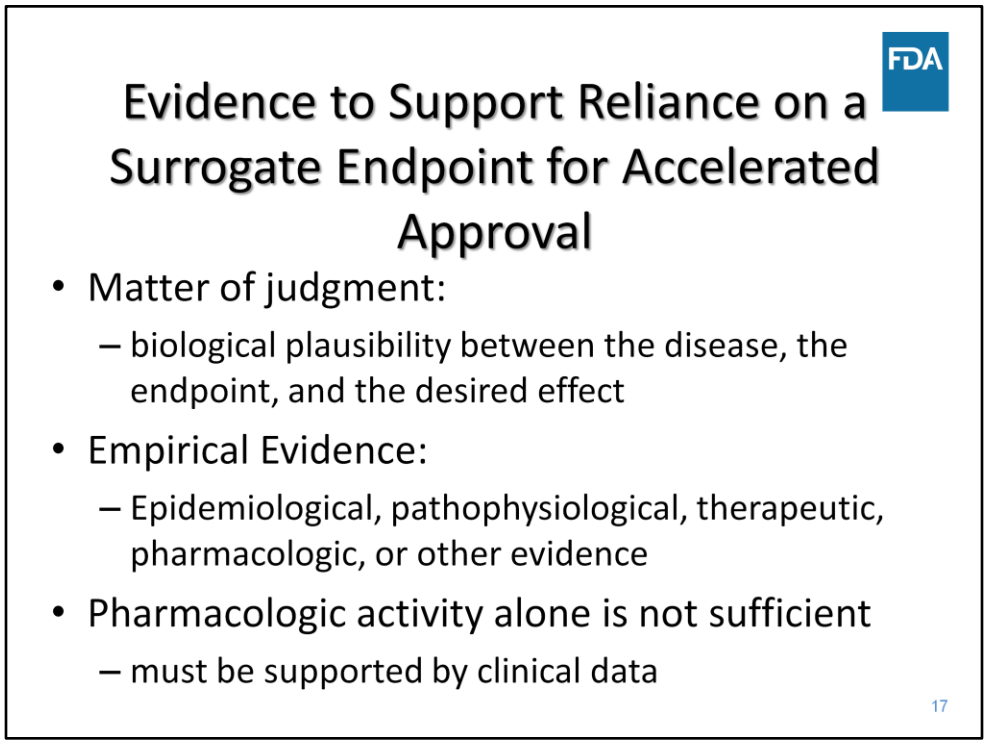
It is important to distinguish a surrogate from a correlate.
Correlates are useful for disease diagnosis or assessing prognosis – an example of a correlate that is useful for diagnosis is prostate-specific antigen or PSA in prostate cancer, however PSA levels do not predict symptoms or death.

In order for a surrogate endpoint to meet the mark, it needs to be
MEASUREABLE
SENSITIVE
And most importantly
ON the PATHWAY to a clinically meaningful endpoint



The provisions of FDASIA (the most recent update to the law) facilitate a somewhat broader use of accelerated approval to expedite patients' access to important treatments for serious conditions allowing (not yet validated) surrogate endpoints or intermediate clinical endpoints considered reasonably likely to predict ultimate clinical benefit.

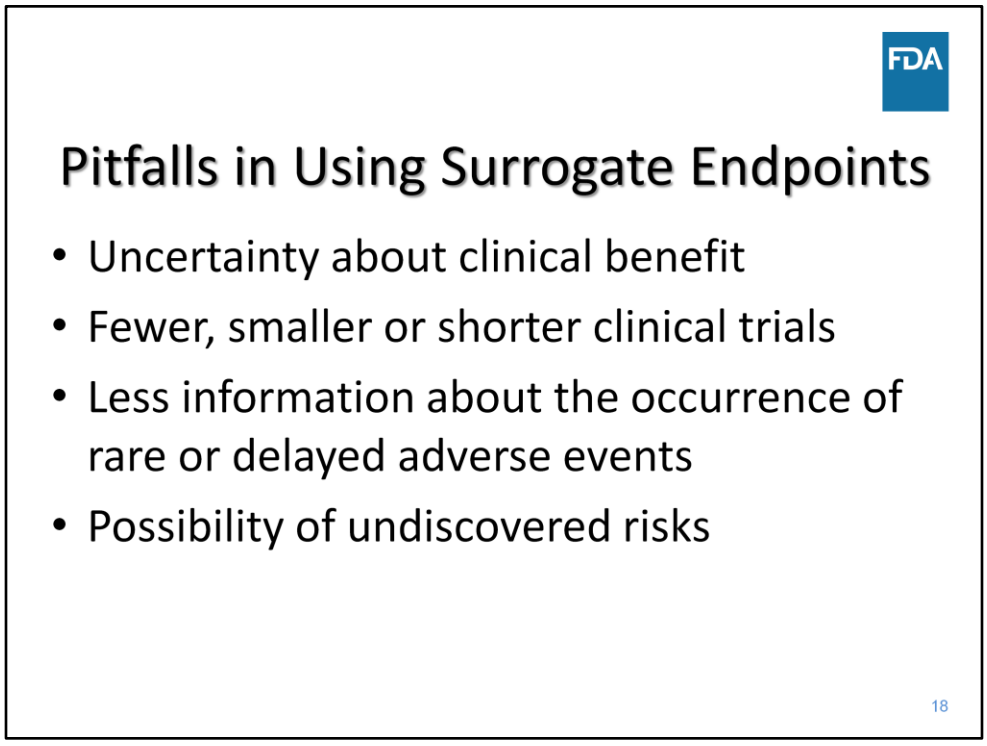
An example of an intermediate clinical endpoint is the relapse rate in multiple sclerosis. A product was approved based on a large therapeutic effect on relapse rate through approximately 13 months of treatment, but where there was uncertainty about the durability of the observed effect. Under accelerated approval, the sponsor was required to continue the existing trials into the postmarketing period to confirm durability of the observed effect at 2 years.



Determining whether an endpoint is reasonably likely to predict clinical benefit is a **matter of judgment** that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect and the empirical evidence to support that relationship.
The **empirical evidence** may include ". . . epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools."
Evidence of **pharmacologic activity alone is not sufficient**, however. Clinical data should be provided to support a conclusion that a relationship of an effect on the surrogate endpoint or intermediate clinical endpoint to an effect on the clinical outcome is reasonably likely.

In making the judgment as to whether a drug's effect on a given endpoint is reasonably likely to predict clinical benefit, FDA considers all relevant evidence and may consult external experts, as needed. (from guidance)

The extent to which a drug's effect on the surrogate endpoint is known to predict an effect on the disease either because the effect is on the causal pathway or because it correlates with clinical outcomes is critical.



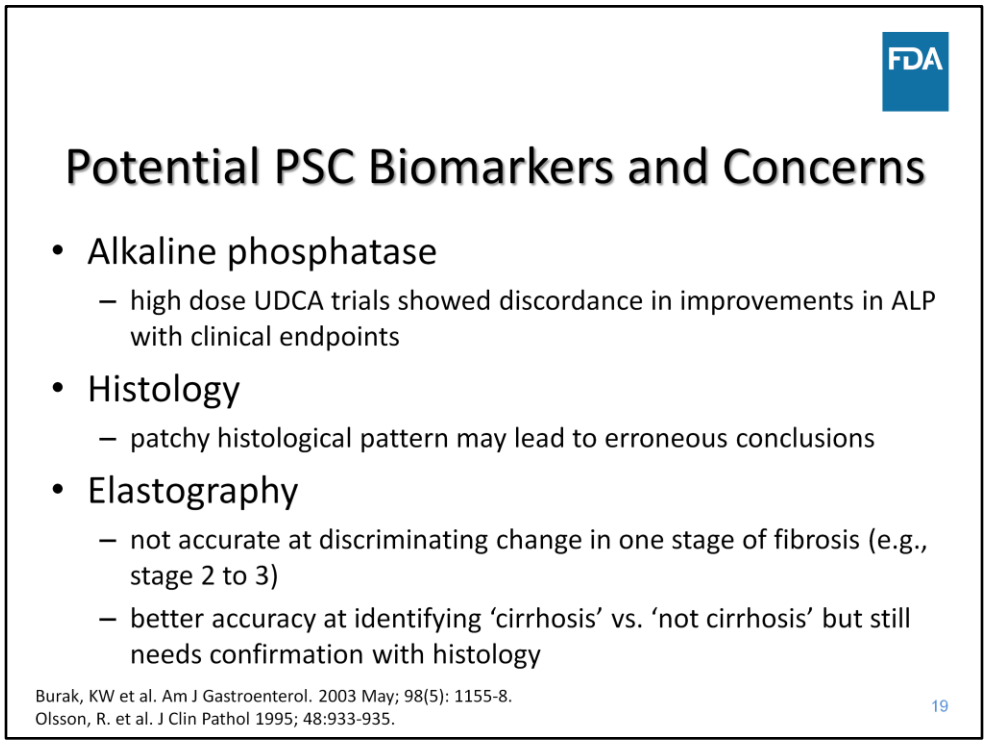
When using surrogate endpoints or intermediate clinical endpoints, the advantage of fewer, smaller or shorter clinical trials is also its principal risk…

compared to traditional approval pathway, the accelerated approval pathway trials are not big or long enough to obtain adequate safety information. In smaller and shorter trials, there is less information about the occurrence of rare or delayed adverse events.

Uncertainty about whether clinical benefit will be verified and the possibility of undiscovered risks are the primary reasons that accelerated approval is reserved for drugs intended to treat a serious condition and that appear to provide a meaningful advantage over available therapy." (from guidance)

AND THEREFORE, trials of surrogate endpoints may sometimes be misleading as to the true net worth of an intervention.

There are examples of where a plausible surrogate that showed improvement with treatment resulted in an overall poor outcome for the patient. Some of these unexpected outcomes may be from off-target effects of a drug.

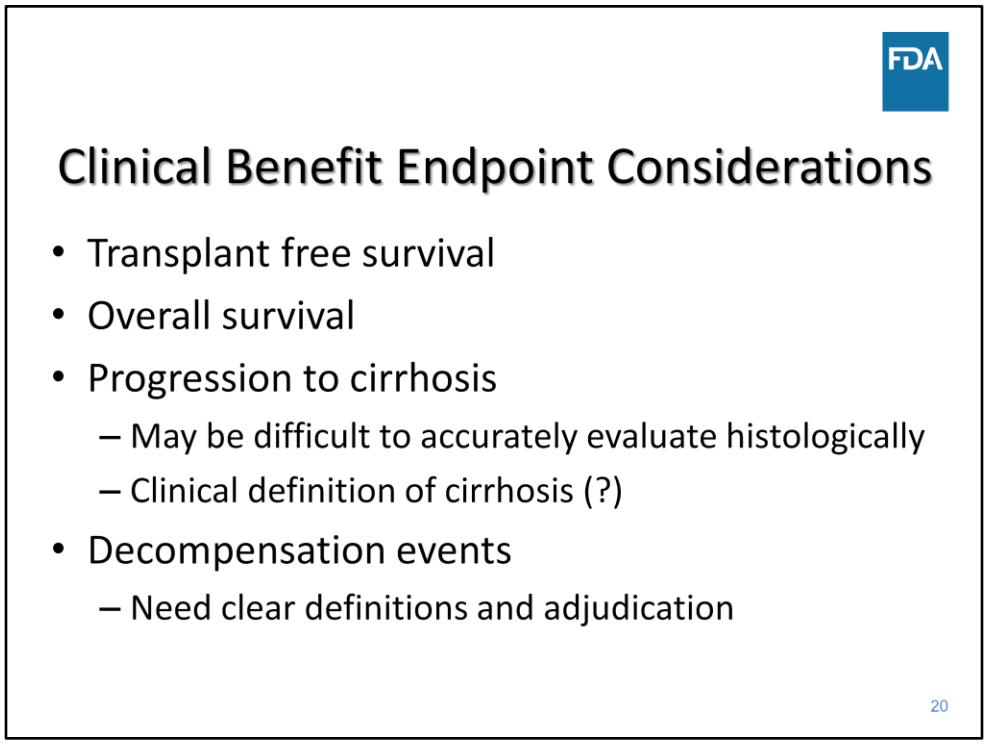


One of the major challenges in designing clinical trials for PSC is the lack of biomarkers that appear to be reasonably likely to predict clinical benefit. Some of the biomarkers being considered are:

Alkaline phosphatase which was not shown to predict **improved** outcomes in the high dose UDCA trials in PSC; therefore, its use in future PSC clinical trials is problematic and would not be acceptable to the Agency as a **standalone** surrogate (in isolation) at this time.

Histology as a biomarker is problematic too because of the patchy nature of the fibrosis pattern within the liver in PSC.

Elastography has been approved by FDA. But the testing was performed on phantoms with known attenuations.
There is considerable literature that shows it is not accurate in discriminating stages of progression of fibrosis, for example discriminating stage 2 from stage 3. There may be value in evaluating cirrhosis; however, there is lack of data on its use in PSC at this time.



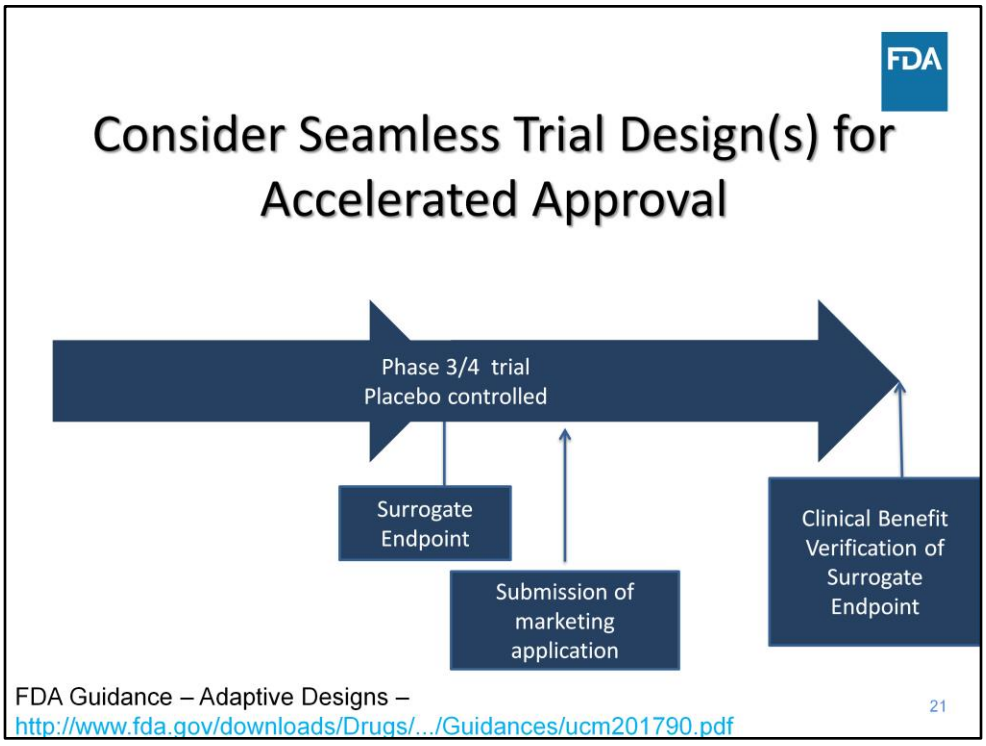
Under accelerated approval a trial to verify and describe the clinical benefit of the treatment generally must be underway at the time of marketing approval. Therefore endpoints that measure the clinical benefit to patients are necessary.

Overall survival and transplant free survival are good measures of clinical benefit; however, they can take many years to reach statistical significance in a trial in PSC.

Another potential endpoint can be progression to cirrhosis, but because of the patchy fibrosis pattern, this can be a problem.

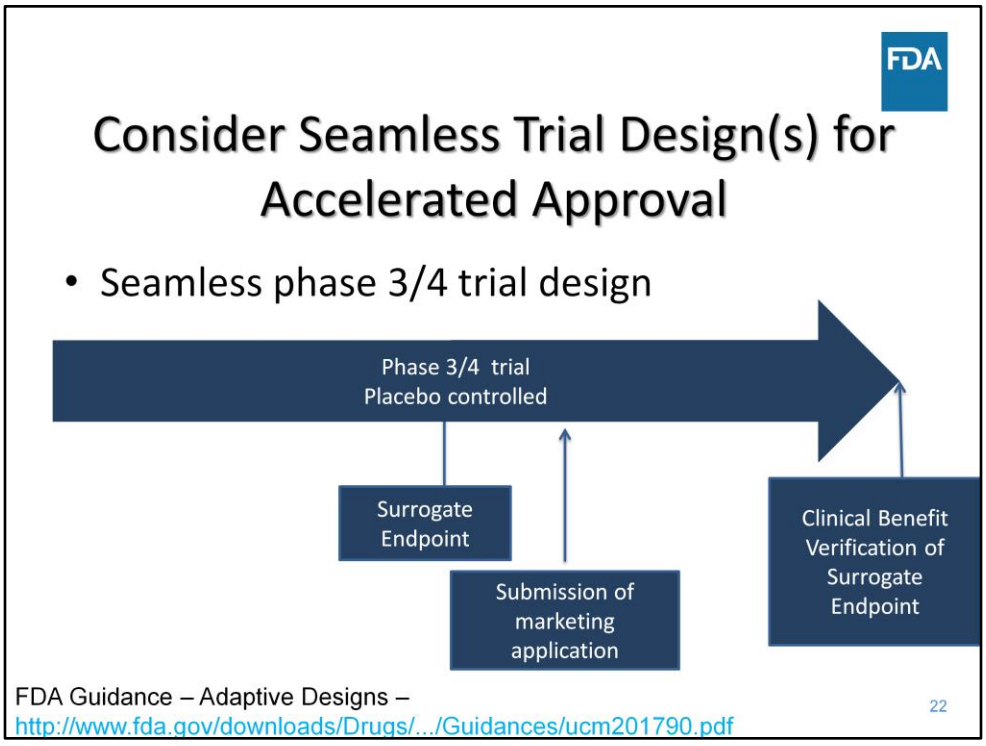
Although a definition of cirrhosis in PSC has not been established at this time, there is potential that such a definition can be developed that would be acceptable to the Division.
This definition should be accurate, and ideally, highly sensitive and specific in detecting PSC patients with cirrhosis.

Decompensation events can also be used as measures of clinical benefit; however these decompensation events need to be clearly defined and adjudicated by an independent blinded committee of experts.



It cannot be stressed enough, Accelerated approval will require that a phase 4 trial be underway at the time of marketing approval to verify and describe the clinical benefit.

This verification, phase 4 trial can be a separate trial, but generally with diseases with a long natural history such as PSC, it may be more efficient to use a seamless design [click] in which the patients are rolled over from the phase 3 to the phase 4 trial.



Needless to say, these trials require forethought. They need to be planned far in advance with a Statistical Analysis Plan submitted prior to trial initiation.

Seamless Trial Design(s) for Accelerated Approval

- If a seamless 3/4 trial design is intended; in order to control the study-wise type I error rate, the overall alpha of 0.05 needs to be adjusted (e.g., 0.01 for phase 3 and 0.04 for phase 4 when two trials are conducted)
- If a single seamless phase 3/4 trial is conducted, a smaller alpha less than 0.05 may be considered necessary if there will be a single phase 4 trial submitted to verify the benefit.

FDA Guidance - Providing Clinical Evidence of Effectiveness for Human Drugs and biological Products
https://www.fda.gov/ohrms/dockets/dockets/98p0311/Tab0035.pdf

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For seamless trial designs, in order to adequately control for type I error rate, you will need to adjust or split the overall alpha between the two trials or use a small alpha less than 0.05 if a single phase 4 trial is planned to verify clinical benefit.

Challenges with Accelerated Approval Trials

- Need to plan far in advance with a Statistical Analysis Plan submitted prior to trial initiation
- Retention of patients in a placebo controlled trial after marketing approval
  - Placebo control is best to assess differences in safety and efficacy outcomes
  - Leveraging a historical control is a potential option, if an adequate historical control database can be identified

FDA Guidance - E10 Choice of Control Group and Related Issues in Clinical Trials
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073139.pdf

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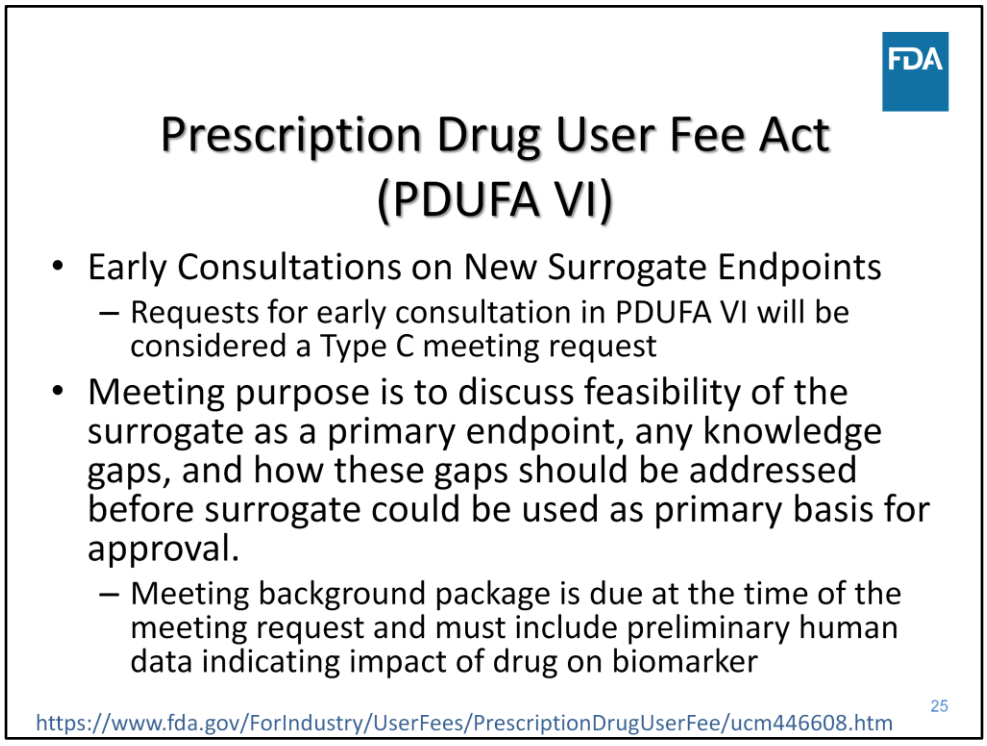
Again, there is a need for post-market confirmatory trial demonstrating clinical benefit if a product is approved under this route;

This pose additional challenges for accelerated approval trials, such as retention of patients in a placebo controlled trial after marketing approval.
in general it is the Agency's view that a placebo arm is STILL feasible for these confirmatory trials because we have clinical equipoise – it is unknown whether the drug provides a clinical benefit.

Using historical control is a potential option and good in theory…however, finding an adequate historical control database is difficult. In fact, there are no good natural history data for PSC at this time. This option is not likely to be practical.



This October, Congress renewed the prescription drug user fee act, and recognizing the increasing need and demand, in the updated provisions, PDUFA 6 will establish a new Type C meeting dedicated to discussing surrogate endpoints. It will be a formal meeting designed to tap the expertise in the agency and require preparation of a specialized briefing package, including human data at a tolerable dose showing responsiveness of the biomarker in question. Processes for fielding these requests are evolving and Sponsors can check with RPMs for further details.

Summary

- PSC is a complex disease
  - There is no single biomarker that is a clear standalone candidate surrogate that is reasonably likely to predict clinical benefit
  - Consideration should be given to developing a composite of multiple biomarkers

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I don't have to tell you this. PSC is a complex disease.

There is no single biomarker that is a clear standalone candidate surrogate that is reasonably likely to predict clinical benefit

Consideration should be given to developing a composite of multiple biomarkers

Summary (2)

- PSC has a long natural history course prior to reaching clinical endpoints:
  - Accelerated approval is a potential drug approval pathway, provided that a surrogate endpoint reasonably likely to predict clinical benefit can be identified
  - Adaptive trial designs could be leveraged in clinical development programs

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Because PSC has such a long natural history course prior to reaching clinical endpoints:

Accelerated approval is a potential drug approval pathway, provided that a surrogate endpoint reasonably likely to predict clinical benefit can be identified AND

Adaptive trial designs could certainly be leveraged in clinical development programs for PSC.


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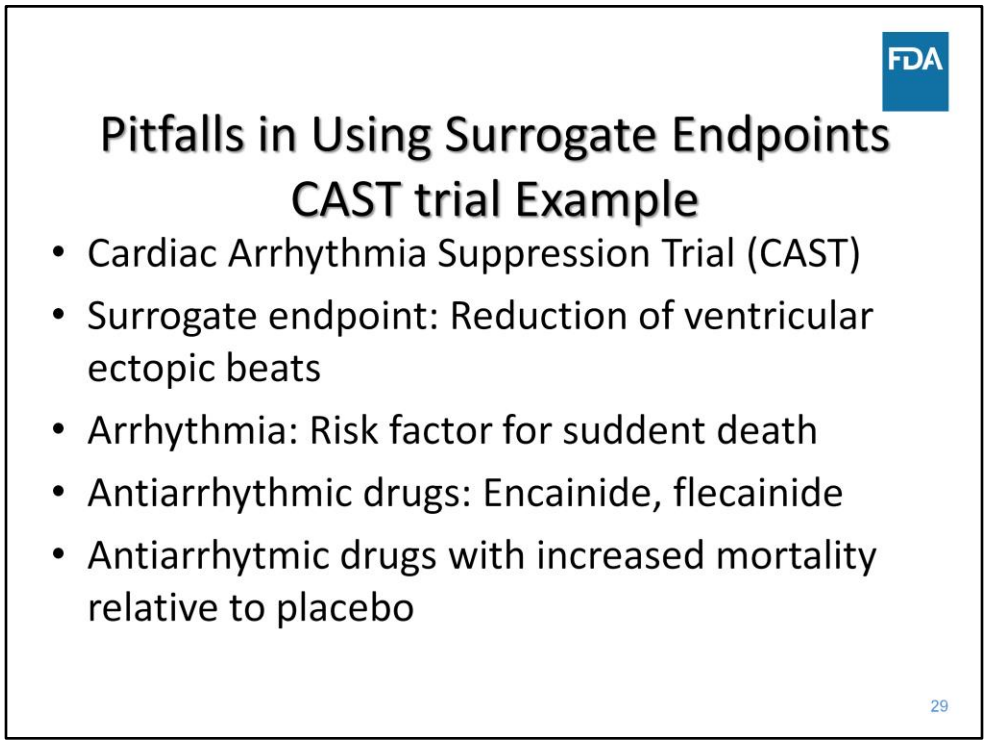

One such example is the increased mortality seen with encainide, flecainide and moricizine treatment in the CAST (Cardiac Arrhythmia Suppression Trial) trials despite successful suppression of premature ventricular contractions (PVCs).

Another recent example is the increased mortality seen with the drug torcetrapib despite elevating HDL.

Examples of surrogate markers may not always be a good pedictor and have to be validated extensively before being used in a regulatory setting.
IN the Cardiac Arrhythmia Suppresion Trial (CAST) that evalauted effect of encainide, flecainide and moricizine on survival of patients who had MI and had >10 premature ventricular beats per hour. Reduction in ventricular ectopic contraction used as a surrogate endpoint decreased mortality.
Flecainide in post-AMI - SEP picked because arrhythmia was a risk factor for sudden death
Antiarrhymic drugs actually TRIPLED the death rate relative to placebo.

Reduces ventriular ectopic beats
Increases mortality (CAST trial NEJM 1991)

Ibopamine in severe HF
Improves cardiac function

Increases mortality (PRIME II trial, Lancet 1997)

Torcetrapib in dyslipedemia
Improves lipid profile
Increases mortality (ILLUMINATE, NEJM 2007)