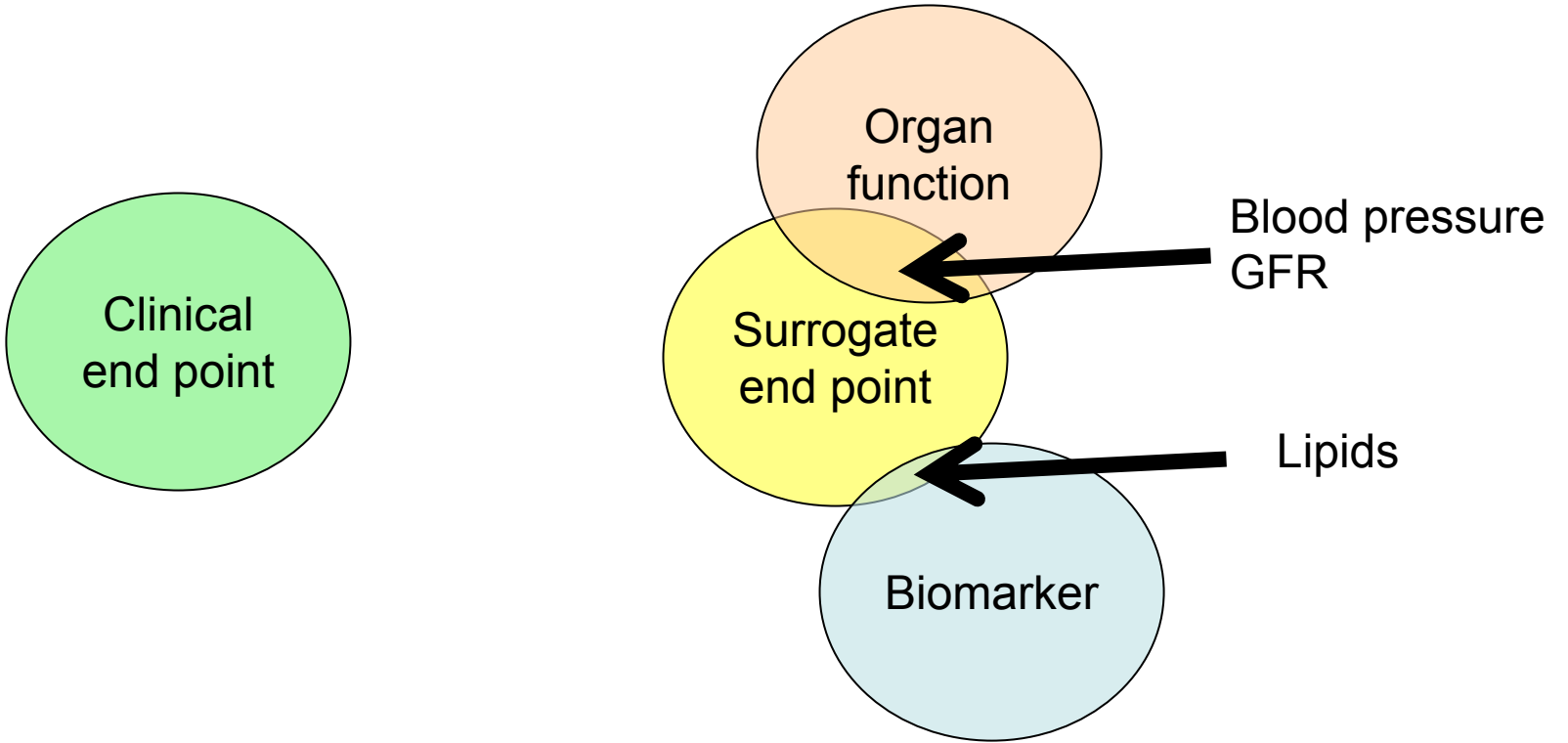


# The Use of Biomarkers for FDA Regulatory Decision-Making— Cardio-Renal

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# Terminology

- Clinical end point = thing of interest to patients (death, hospitalization, symptoms, activities of daily living)
  - Measures of these (SF36, 6MW, NYHA) may be good or bad, but they are not surrogates
- Surrogate end point = functional assessment or biomarker that reliably predicts clinical end point
- Organ function
- Biomarker = soluble tissue product



# Blood pressure

- Surrogate end point
  - Supported by
    - Epidemiological studies
    - Interventional studies with a large number of classes
- Effect size matters (but is rarely an issue)
  - Small effect won't be useful in achieving goals
  - Would require larger safety database

# Myocardial infarction

- Surrogate event
- Myocardial necrosis large enough to be likely to lead to real clinical events
- Magnitude assured by
  - Clinical symptoms
  - ECG changes of a certain magnitude
  - Enzyme changes of a certain magnitude
- Magnitude setting is
  - Empirical
  - Depending on other aspects of the clinical setting
- Small differences in magnitude may not predict benefit

# Progression of renal disease

- Surrogate end point
- Organ function loss large enough is likely to result in real clinical events (ESRD, death)
  - Assessed by GFR
    - Serum creatinine
      - Small changes
        - » May be reversible (hydration, hypertrophy)
        - » May not represent renal function (secretion)

# Biomarkers as part of the definition of an end point

- Component of definition of event
  - Myocardial infarction = { Clinical presentation + ECG + Enzymes }
- Component of composite end point
  - Diabetic nephropathy: Progression = { Serum creatinine ↑ | ESRD | Death }
  - Amyloidosis: Progression = { Nephrosis (proteinuria) | ESRD | ... }

All biomarker components require an effect larger than some threshold.

# Subparts H, E

- 21CFR314 (Subpart H; Drugs)
- 21CFR601 (Subpart E; Biologics)
- New drugs to treat serious or life-threatening diseases
- Meaningful therapeutic benefit
- Surrogate end point reasonably likely to provide clinical benefit
- Subject to additional studies to show benefit

# Subpart H use

## CDER Approvals

| Year | N |
|------|---|
| 2003 | 5 |
| 2004 | 3 |
| 2005 | 4 |
| 2006 | 2 |

- Last Cardio-Renal approval was Remodulin (PAH) in 2002\*.
- Ensuring phase 4 study completion is big problem. Previous approval was 1996—still waiting!
- Ideal is phase 4 follow-up of fully enrolled study

\*Based on post-hoc combination of two indices of clinical benefit

# Cautionary tales

- Antiarrhythmic drugs and sudden death
  - Cardiac Arrhythmia Suppression Trial in patients with asymptomatic non-life-threatening ventricular arrhythmias – higher 10-month mortality on encainide/flecainide than on placebo.
- Inotropes in heart failure
  - PDE3 inhibitors
  - Digoxin (at best neutral)
- (These all have functional or symptomatic benefits, so closer to outcome than markers.)

# Benefit by biomarker

- More tenuous than an end point relying on organ function
- Still have to r/o harm or unintended effects
- Even for a marker considered a validated surrogate (lipids), much less one “reasonably likely” to predict benefit, safety concerns will probably dominate study size.

# Markers for risk

- Less stringent validation
  - Biological plausibility
  - Relationship to pathogenesis
  - Effects on marker track clinical effects...
  - ...at least sometimes
- Directionality is important
  - $\Delta\text{SCre} -0.3$  – Does it matter?
  - $\Delta\text{SCre} +0.3$  – Assume it is bad

# Roles for biomarkers

- Component of benefit
  - Generally hard
  - Still associated with large sample sizes
- Assessment of risk
  - Pre-clinical decision-making
    - Usually unapparent to FDA
  - Dose ranging
    - Needs plausibility (and we still recommend D-R in phase 3)
  - Enrichment
    - OK, but may limit generalizability
  - General safety screening