PROs for Drug Development in Chronic Kidney Disease

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Disclaimer

The views expressed here represent my opinions and do not necessarily represent the views of the FDA.

Overview

- Stagnation in drug development
- Drugs used and approved for use in patients with renal disease
- Patient reported outcomes measures as clinical endpoints and things to consider
- Viewpoint on PROs as a way forward for the development of drugs for PCKD, nephrotic syndrome and anemia of kidney disease

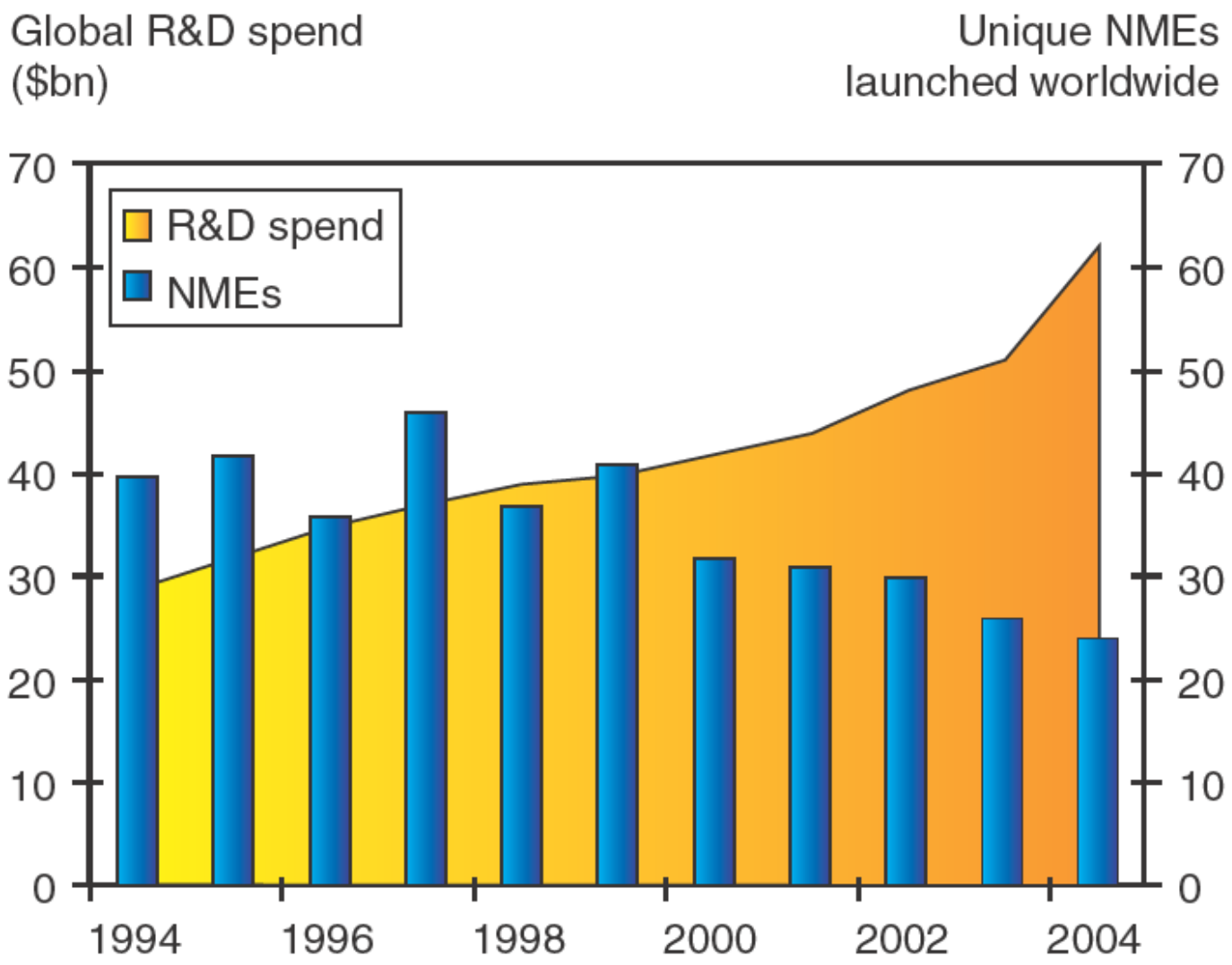


Figure 1

Comparison of global pharmaceutical industry research and development investment and global output of new molecular entities. Source: Hoekema A. 2007. Sharing risks and rewards—basis for a turnkey pharma-biotech alliance in osteoarthritis. *Drug Disc. World* Spring:54

PROBLEMS in DRUG DEVELOPMENT

- COSTS TOO MUCH MONEY
- TAKES TOO MUCH TIME

FDA CRITICAL PATH INITIATIVE

- The Critical Path Institute was formed in 2004 to help support collaborative efforts among stake holders at FDA, NIH, academia and industry
- Mission was to find a better path forward for drug development through the use of biomarkers of toxicity/safety
- More recently, through the use of Patient Reported Outcomes Measures

Approved Drugs Used in the Treatment of Kidney Disease

- Antihypertensive Drugs
- ACEs *
  - ***Diabetic Nephropathy:*** CAPOTEN is indicated for the treatment of diabetic nephropathy (proteinuria >500 mg/day) in patients with type I insulin-dependent diabetes mellitus and retinopathy. CAPOTEN decreases the rate of progression of renal insufficiency and development of serious adverse clinical outcomes (death or need for renal transplantation or dialysis).

*Approved for use in patients with CKD

Approved Drugs Used in the Treatment of Kidney Disease (cont.)

- ARBs*
  - AVAPRO is indicated for the treatment of ***diabetic nephropathy*** with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension. In this population, AVAPRO reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation)

  - COZAAR is indicated for the treatment of ***diabetic nephropathy*** with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, COZAAR reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation)

*Approved for use in patients with CKD

Approved Drugs Used in the Treatment of Kidney Disease (cont.)

- Diuretics for nephrotic syndrome
  - Chlorthalidone is indicated for edema of *nephrotic syndrome*.
  - LASIX is indicated in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.
- ESAs for dialysis patients*
  - PROCRIT®
  - Aranesp®
  - Epogen®
  - Indicated for the treatment of anemia associated with CRF, including patients on dialysis and patients not on dialysis.

*Approved for use in patients with CKD

Approved Drugs Used in the Treatment of Kidney Disease (cont.)

- IV Iron for dialysis patients*
  - INFeD® (iron dextran)
  - Dexferrum®
  - Ferrlecit®
  - Venofer® (iron sucrose or iron saccharate complex) by American Regent.
  - Indicated for iron deficiency anemia, particularly in patients with end-stage renal disease undergoing hemodialysis and receiving epoetin therapy.
- Phosphate binders*
  - PhosLo is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.
  - FOSRENOL® is indicated to reduce serum phosphate in patients with end stage renal disease.
  - Renvela® (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.

*Approved for use in patients with CKD

Approved Drugs Used in the Treatment of Kidney Disease (cont.)

- Vitamin D
  - Ergocalciferol Capsules, USP are indicated for use in the treatment of hypoparathyroidism, refractory rickets, also known as vitamin D resistant rickets, and familial hypophosphatemia.
  - Cholecalciferol is indicated for prevention of osteomalacia when there is insufficient dietary vitamin D uptake and/or insufficient sun exposure
- Hemodialysis and replacement solutions*
- Peritoneal dialysis solutions*
- NAC and Bicarbonate for preventing CIN
  - Approved for use in patients with CKD
- Chemotherapeutic and biologic agents for treatment of SLE

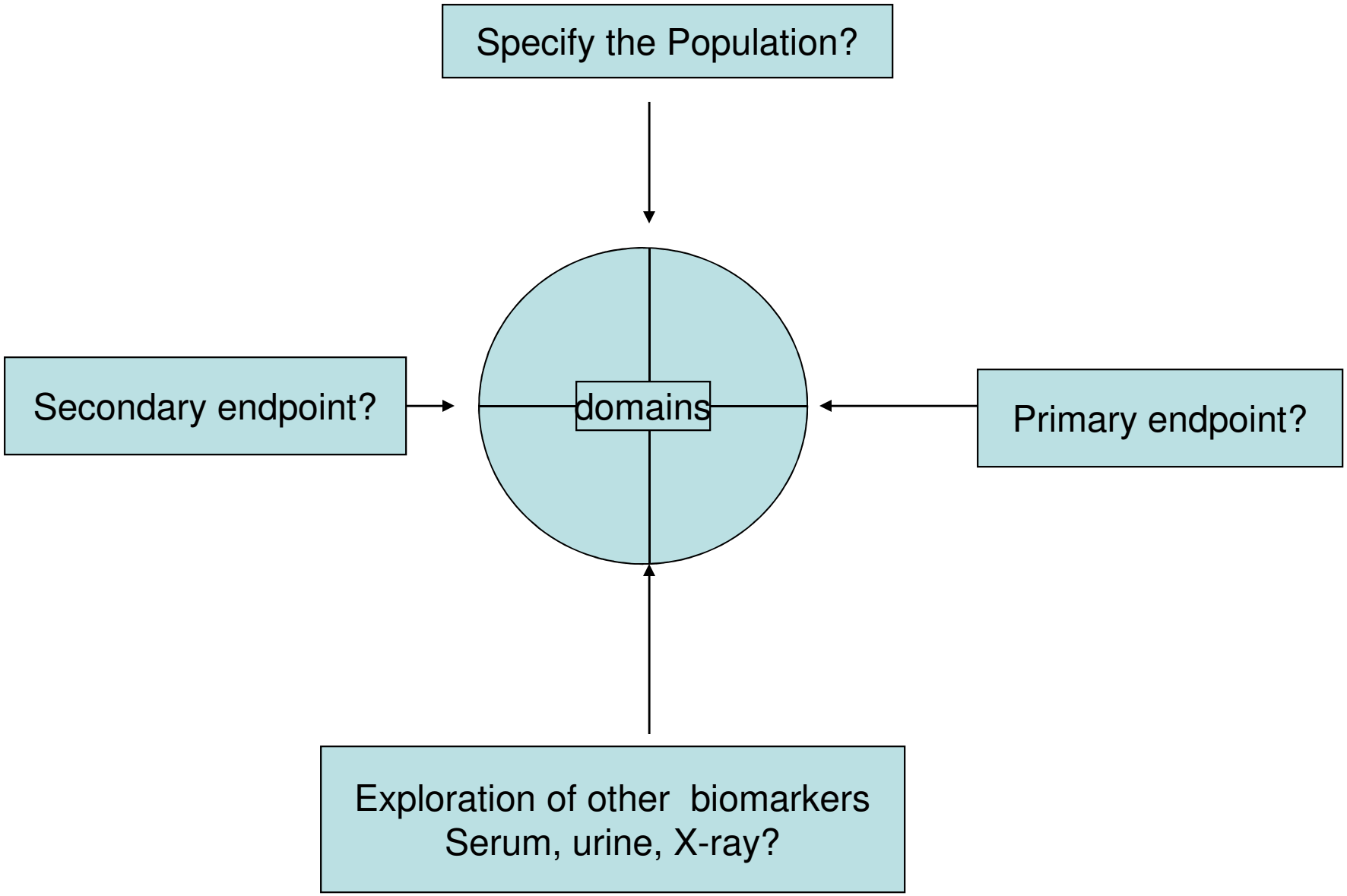
Chronic Kidney Diseases where Treatment is Lacking and Efficacy Endpoints are Challenging

1. PCKD
2. Nephrotic Syndrome
3. Anemia of Renal Disease

PRO instruments

- PRO instruments should be designed to provide information to patients and their health care providers about the specific clinical benefits of drug treatment so that potential risks and benefits can be weighed

- PRO instruments do not necessarily have to measure something that is on the causal pathway of the disease because they can stand alone as clinically meaningful endpoints within certain contexts – that said, secondary pharmacodynamic endpoints are important to support approval


Specify the Population?
Secondary endpoint?
domains
Primary endpoint?
Exploration of other biomarkers
Serum, urine, X-ray?

PCKD Efficacy Endpoints

- Time to Serum Creatinine doubling (or close to doubling) or time to dialysis or death or other meaningful clinical endpoints (how a patient feels, functions or survives) are acceptable endpoints for clinical trials
- Kidney volume is an imaging biomarker that is currently not accepted as a meaningful clinical endpoint because it is not known if preventing or reversing kidney volume changes will have meaningful and lasting effects on kidney function or on how a patient feels, functions or survives
- Currently there are no proteomic or metabolomic biomarkers that can monitor the stabilization or progression of kidney disease

PRO development in PCKD

- A PRO for PCKD would be ideal to assess the way a patient feels and possibly functions during a therapeutic intervention
- Supportive evidence from imaging and serum or urine biomarkers (including durable creatinine changes post withdrawal of drug) would help support approval by providing pharmacodynamic evidence of effect

Nephrotic Syndrome

- Changes in proteinuria do not necessarily predict changes in renal function (In a 4 year longitudinal study in 50 Pima Indians with microalbuminuria, some developed macroalbuminuria and did not have changes in their GFR during the first year of observation)*

- Some ACEs and ARBs in clinical trials were associated with improvement in proteinuria and renal function. It is unknown if there is causal connection or just a correlation. If proteinuria is not on the causal pathway of renal failure, it is difficult to approve drugs based on it.

*Nelson et al, NEJM, 1996

PRO development in nephrotic syndrome

- Nephrotic syndrome can be a very uncomfortable disease because of diuretic resistant edema
- A PRO measure that could show an enduring effect of a drug on the clinical domains pertinent to nephrotic syndrome would be very useful for drug approval. Support for approval could come from reduction in proteinuria or another pharmacodynamic marker of nephrotic syndrome

Anemia of Kidney Disease

- ESAs raise hematocrit, and appear to be associated with tumor growth and strokes
- Mixed results in QOL measures probably because these measures were not developed for the purpose of assessing the important domains for patients with anemia of kidney disease

QOL discrepancies among 3 pivotal ESA trials

Trial	ESA	Trial design	QOL measures	QOL results
Choir	epoetin alpha	2 different targets: 13.5 g/dL and 11.3 g/dL	SF-36 LASA KDQ	All improved in both groups but no significant differences in domains of energy or physical functioning Emotional domain scored worse in 13.5 g/dL target
Treat	darbopoeitin alfa	placebo controlled, target of 13 g/dL with rescue therapy when Hb < 9 g/dL	SF-36 FACT-fatigue	No significant difference between groups Improved the mean+/- SD fatigue score in darbopoeitin alfa treatment group ($p<0.001$)
Create	epoetin beta	early or late anemia correction group early target: 13-15 g/dL late threshold for treatment: < 10.5g/dL late target: 10.5-11.5g/dL	SF-36	Significant difference in domains of energy and physical functioning but patients were not blinded and differences abated overtime despite continued separation of mean Hb levels

PROs in Anemia of Renal Disease

- Hemoglobin is turning out to be a poor surrogate for how patients with anemia of renal disease feel, function and survive
- A PRO could be developed that would explain exactly what clinical domains are being improved by the ESAs so that risks and benefits could be adequately explained in the label

SUMMARY

- PROs may be useful as strategies to address stagnation in at least 3 areas of renal drug development
- There are few drugs approved for use in patients with renal disease.
- We need to develop more drugs that can truly lead to clinical benefits in patients with kidney disease