Is It A Risky Scheme?
Some Ideas For The Pharma Industry Investor

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Elevator Speech – Who Am I

- Tom Crooker's older of two sons.
- Second time presenting to the forum – past performance is no guarantee of success second time around…
- Spent 20+ years in the pharma industry in a variety of different size companies in product development and regulatory roles.
- Undergraduate education in chemistry and earned a law degree mid-career while working full-time.
- Admitted to CA bar on first cycle of bar exam and U.S. Federal Courts in 2015.
- Worked at FDA as a staff counsel and acting team leader in the Office of Compliance in the Center for Drug Evaluation and Research (CDER).
- Left a job as a VP in a global pharma consulting company to start my own solo law and advisory practice focusing on FDA in April 2021.

What Will We Do Today?

- Share my perspective on ***some ideas*** for how investors can better understand the pharma industry and FDA.
- Big topic – we could talk about this for several sessions and careers are made on this subject.
- ***Starting point*** for how to spot issues and start organizing information for analysis.
- Informal and conversational.
- Don't wait to ask questions – and any question is relevant so don't hesitate to ask.
- I'm always open to a new lawyer joke.

Where To Start?

- There are good arguments for starting by looking at how the pharma industry operates drug development and commercial activities.
- No doubt industry owns the initiative and economic incentives to operate…but they can't do business without heavy involvement of the FDA.
- The FDA in some way, shape fashion or form regulates a collection of products that combined constitute about 20% of the country's GDP.
- FDA is the gatekeeper for several major areas of pharma's operations:
  - Clinical trials.
  - Review of applications to market a product and post-marketing applications.
  - Commercial activities including marketing and manufacturing.
- If a firm can't navigate FDA then it can't operate. And investors need to understand FDA too so they can make decisions.
- So we will start with a brief look at the FDA with a focus on drugs.
- But you need to understand both actors to get as complete a "total mix of information" as possible.

What Is The FDA?

- Peter Barton Hutt story – legendary former FDA Chief Counsel. Some classic remarks you should remember (paraphrasing).
  - "FDA is first, foremost and always a federal law enforcement agency."
  - "FDA is not your customer."
  - "FDA culture is like a mosaic."
  - Pattern recognition.
- ***Six*** different "product centers."
- ***Plus*** Office of Regulatory Affairs (field staff).
- All told about 15,000 employees.
- Bottom line: very large de-centralized federal agency.
  - That has consequences inside and outside FDA that challenges investors.
  - Communication and consistency.
- If you want more detail, see the *Fact Sheet: FDA At A Glance* - Fact Sheet: FDA at a Glance | FDA.
- All the publicly available organizational charts are found here - FDA Organization Charts | FDA
  - Less details over time and reorganizations – more challenges to investors.

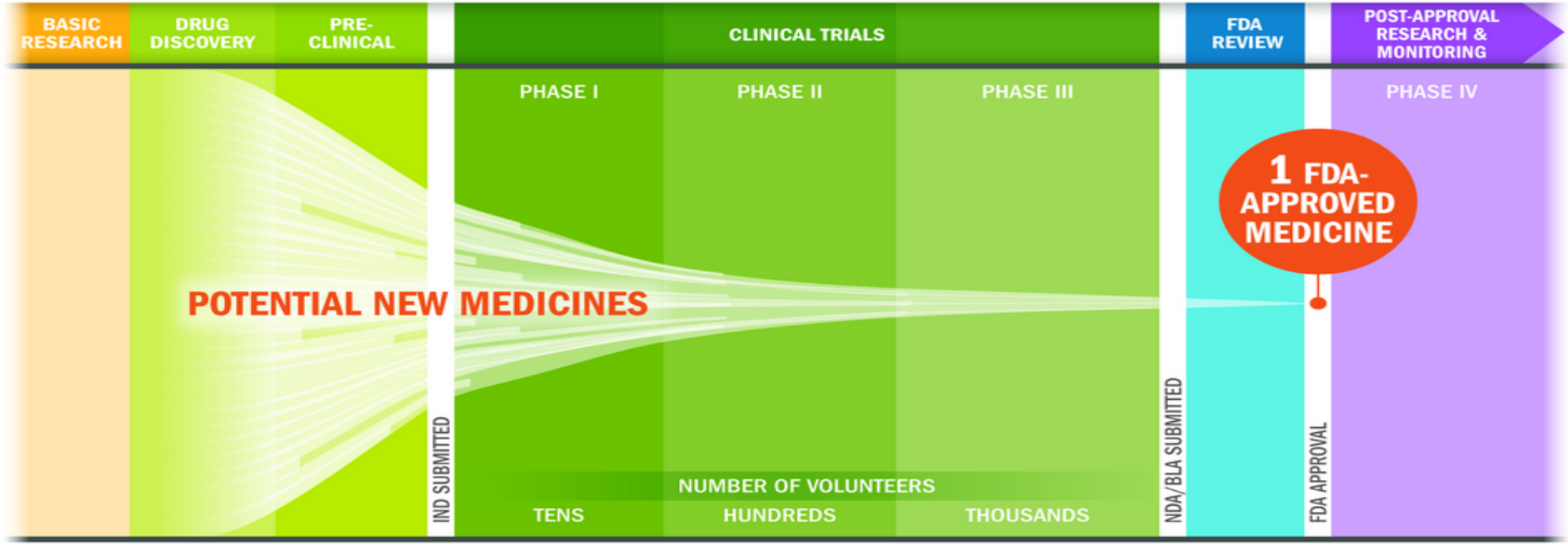
How Does An Investor Make Sense of FDA?

- You don't need to hire a consultant or FDA lawyer…
- But you do need to recognize that are limits on what FDA can publicly divulge
  - Running debate about "greater transparency" but applications are *ex parte* review;
  - Legal limits that constrain FDA.
  - What FDA cannot release but investors want to see.
- There is a large amount of publicly available information – abundance of riches if you know where to look.
- Try to spot the issue – what stage of development and FDA interactions are involved? (more on that in a bit).
- FDA has large amount of discretion – leads to uncertainty.
  - Exondys® 51 & 53.
  - Aduhelm®
- So where can you look to find nuggets of information?
  - "Podium policy" – but beware non-binding advice.
  - Press releases and publications by FDA.
  - FDA policy documents – there are thousands.
  - Enforcement actions such as Warning Letters.
  - FOIA requests – adequate description, scope and time.
  - Most important documents – "summary basis of approvals."
    - Redacted administrative record of the FDA review and approval decision.
    - You can find these here - Drugs@FDA: FDA-Approved Drugs

What Do You Need To Know About Industry (1) ?

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of $2.6 billion.* Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.

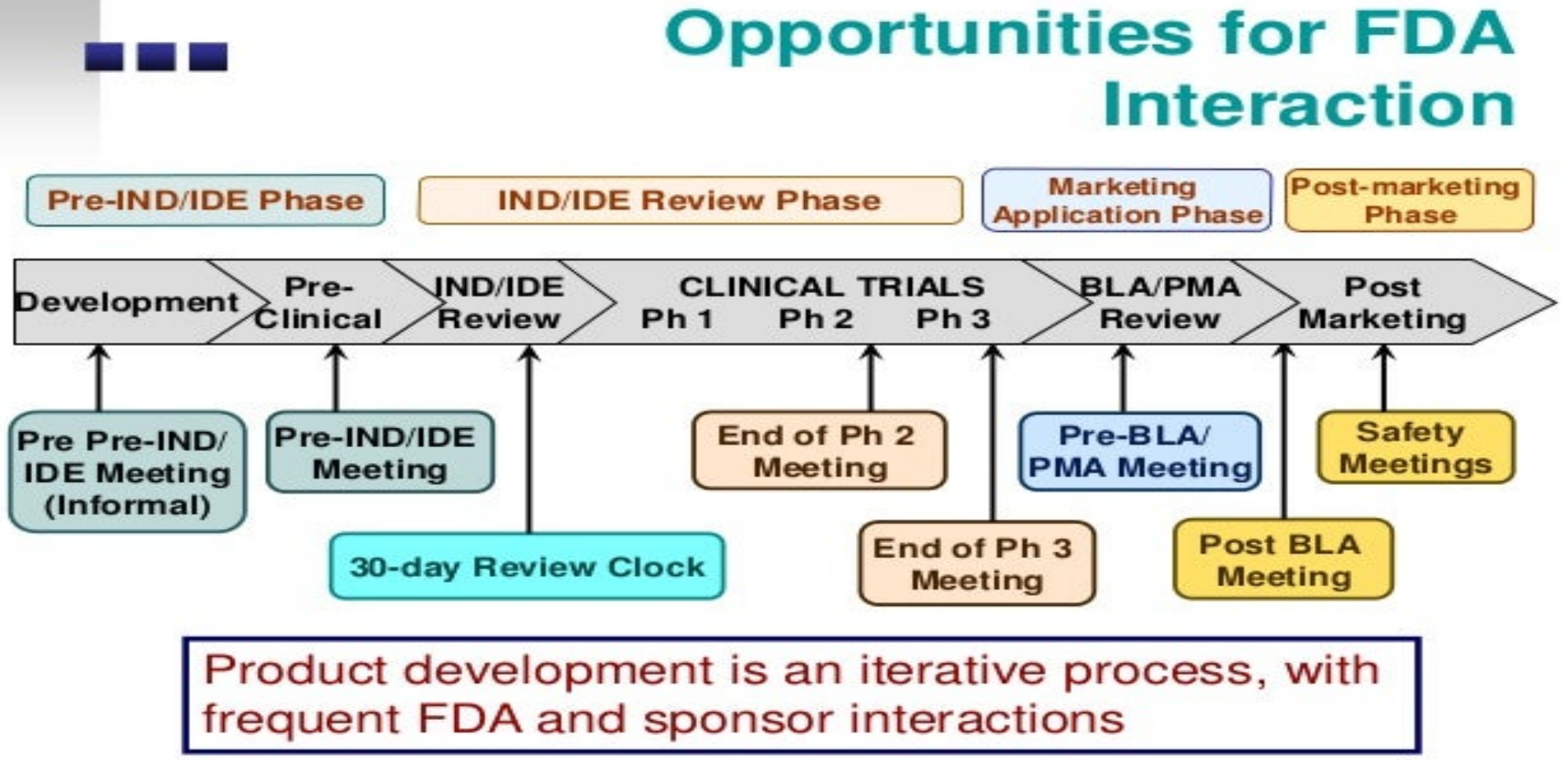


Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf (accessed Jan. 20, 2015).

What Do You Need To Know About Industry (2) ?



What Do You Need To Know About Industry (3) ?

- Large amount of information on those two slides.
- What's the simple message?
  - Large number of drugs in development and marketed (in the thousands).
  - There are numerous times when a company can meet with FDA over the course of years before an application is approved – potential for large amounts of information to be exchanged.
  - And most of those interactions are confidential commercial information that never sees the light of day.
- For publicly traded companies your best source of insight are annual and periodic Securities and Exchange Commission (SEC) filings.
  - Several sources – here is the SEC EDGAR site: SEC.gov | Company Search Page.
  - Focus on management's discussion of risk – some boilerplate language is common.
  - Understand "materiality" for both investors (SEC) and FDA review – that is the most important information.
- Sometimes master supply agreements are attached to SEC filings – manufacturing.
- Press releases – particularly after receiving a Complete Response Letter or FDA inspections.
- Analyst notes – but know how to parse them closely and understand relationships.
- Literature searches – basic and applied science and includes FDA authors.
- FDA enforcement actions – can wreak havoc at any time.
  - Most recent high-profile incident is Abbott & baby formula but not always so visible.
  - Not just manufacturing but also promotional activities – litigation and commercial speech regulation.

Some Rules Of Thumb To Remember (1)

- The “total mix” of information includes understanding FDA and industry.
- FDA is not monolithic and its inherent discretion is significant.
- FDA is a patten recognition organization but that does not extinguish inconsistency at times.
- Recognize that you will only be able to access partial information from FDA and companies get access first and then decide how to handle it.
- Focus on information that is “material” to both FDA and the manufacturer.
  - What information would a reasonable investor and FDA staff consider important in making a decision?
- Relying on past performance as best indicator of future action, the best repository of FDA thinking are the summary basis of approvals.
- SEC filings for publicly listed companies contain important information about management’s view of risk.
- Analyst reports can offer insight but read them in context.

Some Rules Of Thumb To Remember (2)

- If you don't understand the underlying science or technology or there are "hot" areas (such as gene therapy), two choices before diving in:
  - Educate yourself; or
  - Refrain from investing in that particular niche.
- Companies that have lost trust with FDA typically receive greater scrutiny – examples abound such as Ranbaxy (generics) and AveXis (subsidiary of Novartis).
- Product development isn't the only game - don't overlook routine and exigent enforcement for commercial functions. FDA actions can derail a wide swath of a company's operations – "butterfly effect."
- Some FDA actions can have a decade-long affect on a company (typically consent decrees litigated on behalf of FDA by DOJ).
- Pharma is an innovative and risk-taking environment; FDA can – but not always - clash with a slow-moving and risk-averse culture. When FDA acts rapidly the results can be unexpected at times.

Some Rules Of Thumb To Remember (3)

- M&A activity can be very disruptive in industry and at FDA – lack of alignment and gaps. Think Mylan and AveXis again.
- Beware companies that are mired in analysis paralysis – first to market is the goal and optimize the product label over the lifecycle of the drug.
- Sooner or later if a company can't control its supply chain FDA will intervene – results in loss of freedom to operate by a company. Think heparin.
- Don't expect FDA to act at a pandemic pace as normal course of business.
- Commissioners make a difference in culture and priorities – compare and contrast past and present.
- It is impossible to predict what FDA will do but it is possible to understand and anticipate what its reasonable responses will be (probabilities).
- When in doubt, rely on instruments such as sector mutual funds or ETF to spread risk and diversify exposure.