The Regulator as Gatekeeper and Enabler for Drug Development

A South African Perspective

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The Public Health Role of the Regulator

World Health Assembly Resolution 52.19

Urges Member States to:

(1) to reaffirm their commitment to ..... taking all necessary concrete measures in order to ensure equitable access to essential drugs;

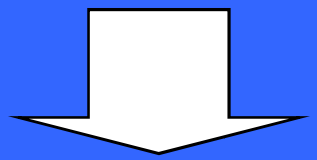
(2) to ensure that public health interests are paramount in pharmaceutical and health policies;

(3) to explore and review their options under relevant international agreements, including trade agreements, to safeguard access to essential drugs

The Public Health Role of the Regulator

Implications for Drug Regulatory Authorities:

- Public health as a priority for regulatory system strategies and decisions
- Ensure safe, effective, quality and affordable drugs
- Improve post-marketing surveillance (PMS) of products in the marketplace



Improved regulatory systems with capacity to meet needs of health professionals and public

Medicine Regulation and Public Health

Good Regulatory Practice requires (1):

- Mission and objectives clearly stated;
- Procedures and outcomes transparent to applicants, health professionals, and public;
- Arguments used to reach decision accessible to the public;
- Reasonable duration of assessment without compromising quality, safety & efficacy
- Regularly assess whether objectives are being achieved

Medicine Regulation and Public Health

Good Regulatory Practice requires (2):

- *Expedite review for orphan and priority public health medicines*;
- Accountability to government, those regulated, and the public;
- Personnel adequately trained, highly qualified and of high integrity;
- Human resource development programme

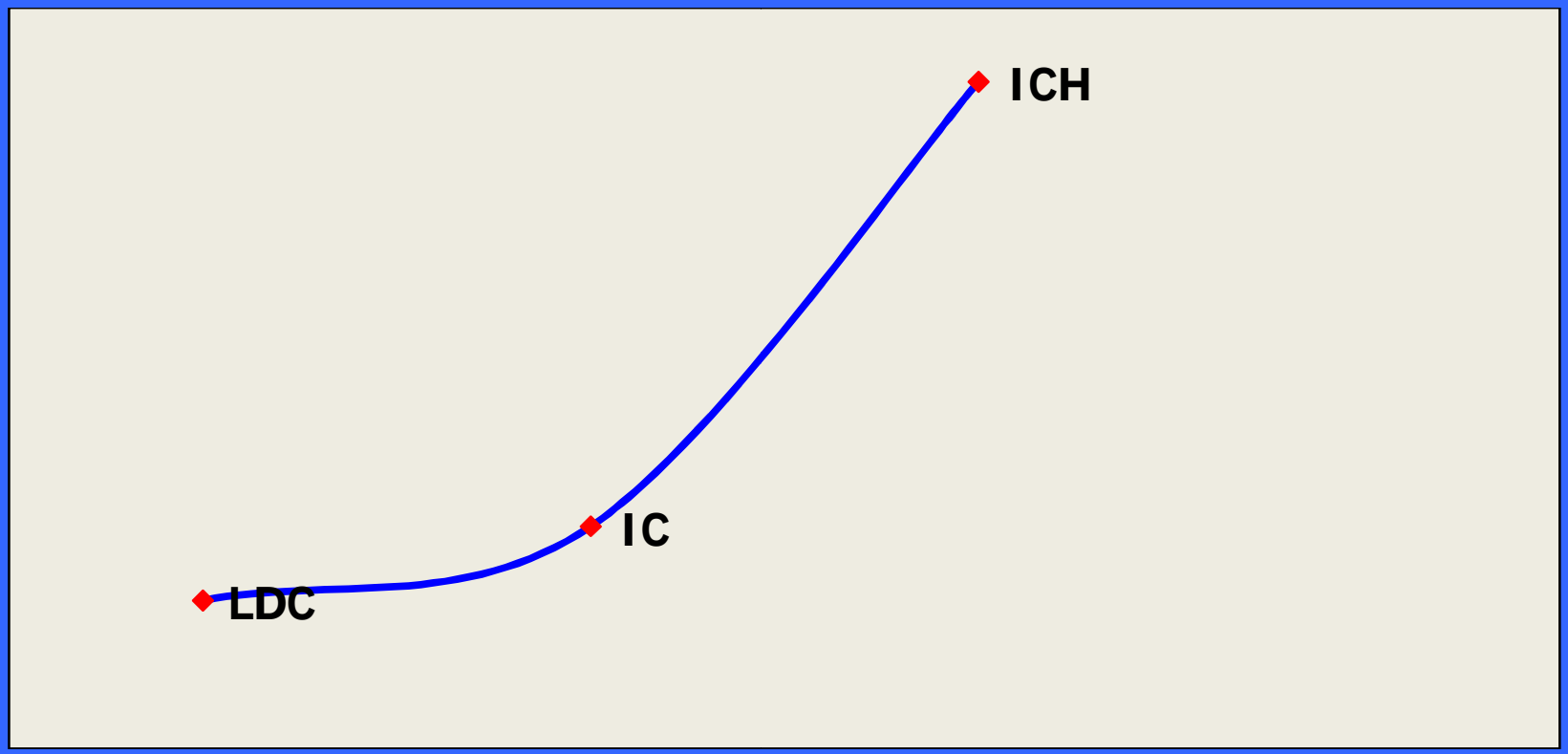
Medicine Regulation and Public Health

Good Regulatory Practice requires (3):

- Mechanisms for appeal and for handling public complaints;
- Access to appropriate knowledge and technology;
- Consumers are provided with accurate and appropriate drug information;
- Mechanisms to ensure quality of operating procedures.

Medicine Regulation and Public Health

Technical Regulatory Requirements and Capacity Gaps



Medicine Regulation and Public Health

‘Stringent’ Regulatory Authorities

- Thousands of highly qualified professionals and external experts;
- Unlimited access to most technologies and knowledge;
- Not resource constrained to the same extent as developing countries.

Medicine Regulation and Public Health

Setting priorities based on available resources:

- Ensure effective market control:
  - Establish list of authorizable marketed products
  - *Prioritise public health relevant products;*
  - Strengthen inspection of manufacturing and distribution
  - Limit number of entry points for imported medicines
  - Establish adequate sanctions for violators
- Establish GMP and GCP requirement for inspections;
- Strengthen pharmacovigilance systems;
- Identify ‘reference’ DRAs for cooperation;
- Focus on regulation and control of generics;
- Build collaboration with academic and research institutions.

MCC Mandate...

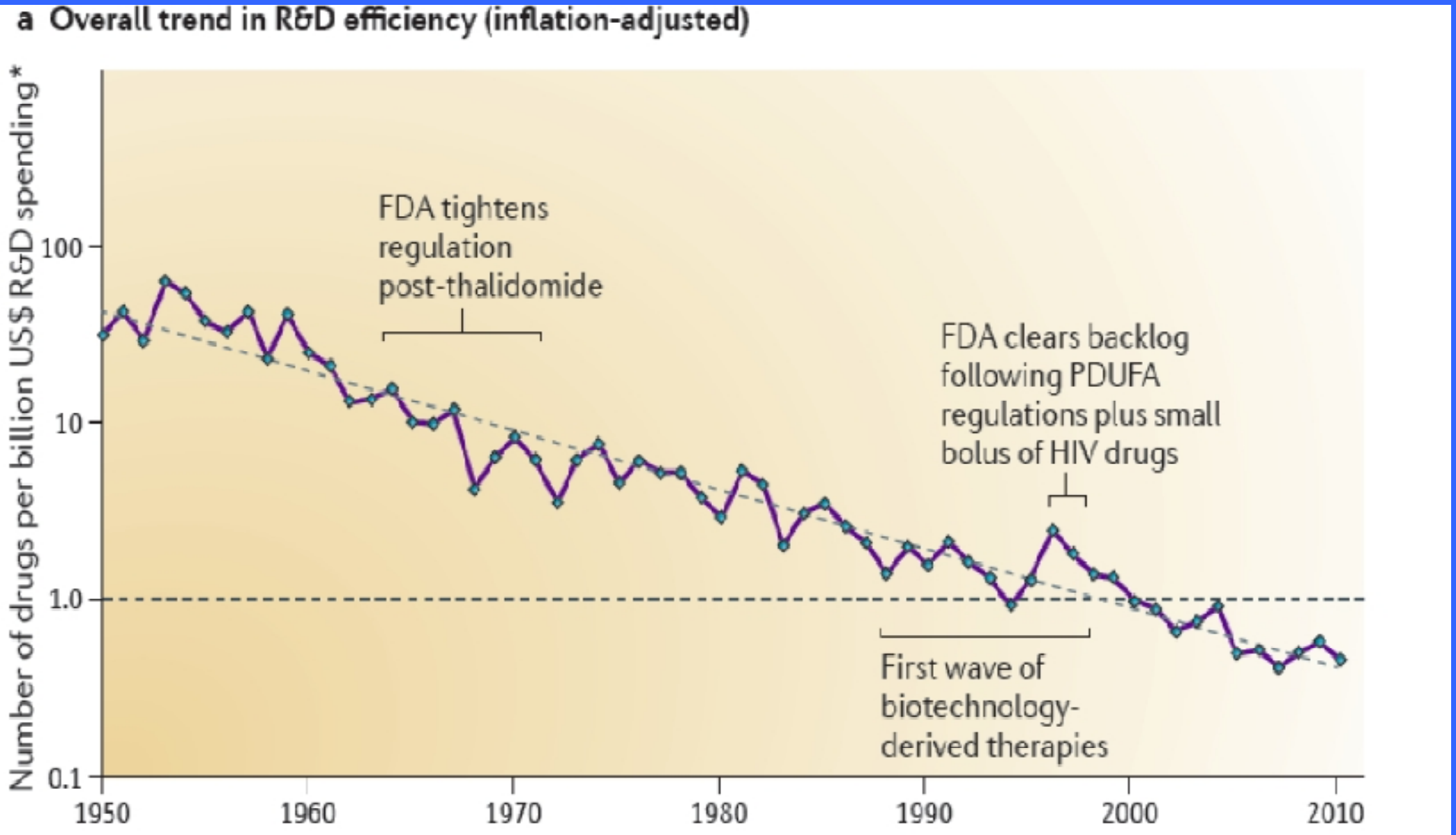
“Safeguard public health through access to safe and effective medicines that are of good quality”

- Timely access to quality medicines
- Effective regulation of medicines
- Good regulatory practices
- Ensure conformity of medicines to set standards of safety, quality and efficacy
- Make objective information available to all in an ethically acceptable manner
- Establish collaborative linkages and partnerships

The Role of Drug Regulatory Authorities

Two distinct objectives:

- Protect patients against ineffective or harmful medicines
  - *Gatekeeper* function and obliges regulators to apply stringent standards of assessment and to deny marketing authorization where deemed necessary
- Protect patients against the consequences of untreated disease
  - requires regulators to *enable* drug development - with a view to ensuring that patients have access as early as possible to safe and effective drugs.



Scannell et al, *Nature Review Drug Discovery*, March 2012.

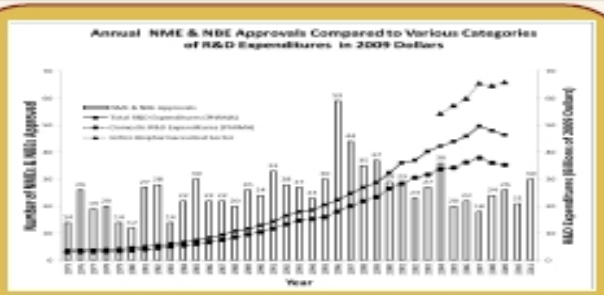
Healthcare Innovation Ecosystem

PATIENTS
Unmet Medical Needs

"Of the 7,000 human diseases, fewer than 300 are of interest to the biopharmaceutical industry, due to limited prevalence and/or commercial potential."

Office of Rare Diseases Research, NIH

PHARMAS
Ususstainable cost of innovation



Burrill & Co. Analysis for PhRMA 2006-2011

Failure to capture full value of innovation for all stakeholders

PROVIDERS
Need better benefit/risk information

"I rarely prescribe a new drug during the first 2 years it has been on the market. There is too much uncertainty about safety during this time.

Neurologist, Boston

REGULATORS
Competing Demands: Innovation & Safety

"Our current regulatory model sets unrealistic expectations for the public that it is possible to eliminate all uncertainty about product safety prior to market approval."

Senior Official, FDA

PAYORS
Skyrocketing costs

"Healthcare spending to reach 25% of GDP by 2025. Reimbursement coverage decisions should be driven by evidence of clinical value."

Congressional Budget Office

Problems in the current Drug Innovation System that need to be addressed

- Patients exposed to unnecessary risks as uncertainty is addressed
- RCTs imperfect predictor of safety/efficacy/effectiveness in use
- Weak information on subgroup specific benefits and risks of drugs
- Liability driven by unrealistic expectations on uncertainty and risk
- Longer times, higher costs, increasing late stage failures in drug development
- Innovation declining, number of new drugs emerging from pipeline falling
- Costs of healthcare system as a whole rising

Would an adaptive drug development pathway tuned for learning and discrimination address some or all of these problems?

Traditional Licensing Approach – Need for a paradigm shift

- Current approach is based on binary decisions. At the moment of licensing, an uncertain experimental therapy is presumptively transformed into a fully vetted safe and efficacious therapy.
- Drug evaluation using a *progressive/staggered/adaptive* licensing approach is part of a continuum and is based on stepwise evaluation under acknowledged conditions of uncertainty.
- Some features include:
  - Limited initial access to patients with best expected benefit/risk ratios
  - Reimbursement and coverage during initial authorization
  - Capture experience on safety/efficacy/effectiveness of drug in use
  - Reassess licenser/sponsor/payer/provider/patient practices using info
  - One size does not fit all – risk-based

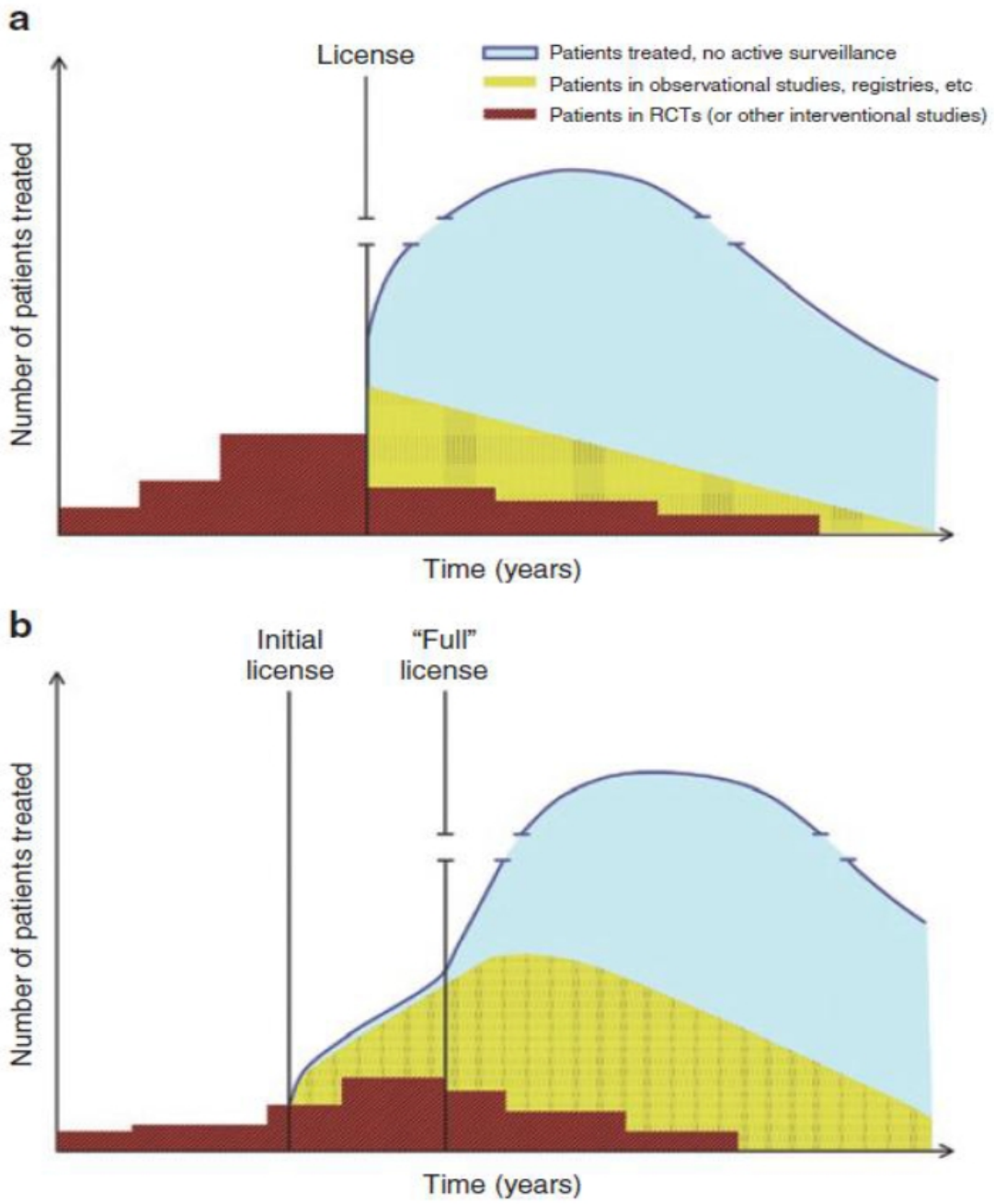


Figure 1 Time course of evidence generation and accrual rates of patients

Evidence Generation and Adaptive Licensing Pathways

- **a) Current:** Pre-approval RCTs; access by patients expands rapidly once approved, but limited ongoing data (e.g from registries or observational studies)

- **b) Adaptive:** fewer patients pre-approval; slower uptake post licensing due to prescribing restrictions; most patients in observational (comparative effectiveness) studies or RCTs after full approval; need for less active surveillance over time

Eichler et al. 2012 CPT

Requirements for Adaptive Pathways to Licensing

- Assumes the “impossibility of understanding effects of drugs at time of traditional market entry” and recommends:
  - Conditional registration
  - Aggressive assessment throughout life cycle;
  - Public–private funding of postmarket assessments;
  - Overhaul of adverse events reporting and investments in pharmacoepidemiology;
  - Authority requires post-marketing reports and conducts full 5-year reviews of new molecular entities.

Institutes of Medicine, Future of Drug Safety (2006)

Experience of Market Access in SA

Priority Public Health Needs

- Communicable Diseases
  - HIV/AIDS, TB, malaria
  - Sexually transmitted Infections
  - Respiratory infections
  - Meningitis
  - Diarrhoeal diseases
  - Childhood diseases
- Non-communicable diseases
    - CVD, diabetes, cancer, asthma, depression, etc

Frameworks for Enabling Access in SA

- Expedited Review and registration
  - Information sharing with other NRAs
- Conditional registration
  - Risk management plans, reporting and dossier updating
- Section 21
  - Investigational products
  - Named-patient based
  - Programmatic access (e.g., BDQ, linezolid)
  - Strict requirements for reporting

Enabling Early Market Access

- Early registration is likely to require collaboration with other regulatory authorities
- Potential approaches include:
  - Information sharing
  - Undertaking collaborative scientific work
  - Common data collection, risk assessment or compliance methods
  - Joint review
  - Developing common or international standards
  - Equivalency or mutual Recognition
  - Harmonization

Early Engagement with Sponsors and Researchers (IND-type process)

- Aimed at avoiding the risk that study results may not satisfy regulatory requirements with resultant delays in licensure
- Provides a mechanism by which MCC is kept informed and can offer scientific advice and recommendations
- Prospective dialogue and formal pre-submission meetings
- Discussion on CMC data and manufacturing expectations, clinical trial design, appropriate study populations, statistical analysis plan, safety issues of potential concern, and regulatory submission requirements
- Develop plans for safety monitoring and post-marketing surveillance

Thank You