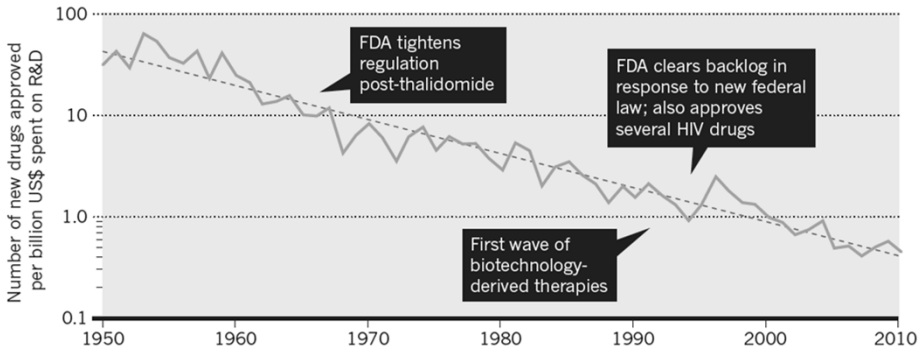
Something Old and Something New: Drug Repurposing from a University Perspective

Webinar Outline

- Is the moment now for drug repurposing?
- What is drug repurposing?
- Why repurpose?
- Blockbuster potential
- Players in drug repurposing
- Key considerations
  - Scientific
  - IP / Patent
  - Regulatory
- Legislation regarding drug repurposing

Productivity Crisis

Falling productivity in the pharmaceutical sector has led to articulation of "Eroom's Law": *Efficiency of research and development of new drugs halves about every nine years.*



Source: N. Nosengo, Nature (2016) 524:314-316

Funding interest - non-profits and government initiatives

•Non-Profits

- Cures Within Reach
  - 80 partners from philanthropy, academia, patient advocacy and the pharmaceutical and biotechnology industry
  - Raised funds for and overseen more than 50 drug repurposing research projects
  - Created 12 repurposed therapies that are either being used off-label by physicians and patients or are undergoing larger confirmatory clinical trials toward commercialization
  - Launched CureAccelerator - an online platform for repurposing research

  http://cureaccelerator.org/

•Federal Government

- NIH National Center for Advancing Translational Science has specific monies dedicated to funding for drug repurposing

  https://ncats.nih.gov/preclinical/repurpose

What is drug repurposing?

Broadly, any of many redevelopment strategies based on the same chemical structure of the therapeutically active ingredient as in the original product (whether ultimately approved or not).

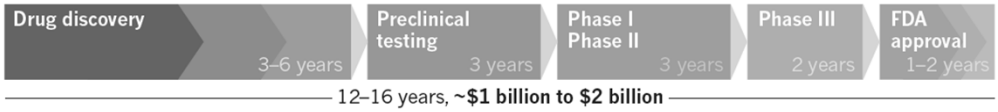
"*Repurposing describes the general concept of branching the development of an active pharmaceutical ingredient, at any stage of the life cycle and regardless of the success or misfortune it has encountered so far, to serve a therapeutic purpose that is significantly different from the originally intended one*."

H.A.M. Mucke, Journal for the Drug Repurposing Community. Drug Repurposing, Rescue & Repositioning 1, 3-4 (2014)

Species within the genus of "repurposing"

- Secondary indications for generic products ("repurposing")
- Expanded indications (product line expansion) for already marketed (FDA) approved products
- Different indications for products shelved due to late-stage efficacy and/or safety failures ("rescue")
- Providing more precise and targeted indications for therapies in clinical trials than those originally selected ("repositioning")
- Changing or adding indications to drugs in preclinical or clinical development ("therapeutic switching")

Why repurpose? Cost and Speed



A SHORTER TIMESCALE

Because most repositioned drugs have already passed the early phases of development and clinical testing, they can potentially win approval in less than half the time and at one-quarter of the cost.

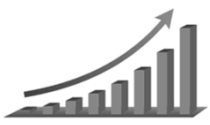
Source: N. Nosengo, Nature (2016) 524:314-316

Caveats on the cost and speed advantages…

- Prior knowledge about the compound - best if no new formulation and/or dosing has to be developed and tested)
- If existing data is sufficiently recent to meet FDA requirements -more credible to the safety aspects of the drug.

Risk and Return

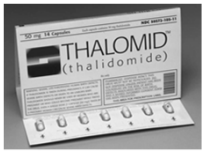
- Lower development risk
  - Safety is known for:
    - Drugs that have been approved by regulatory agency (e.g., FDA, EMA or PMDA)
  - Found to be safe but failed to meet their end points in originally-targeted indications (and as a result were shelved)
- Market for repurposed drugs
  - Some estimates predict $31.3 billion by 2020



Blockbuster Potential

•Thalomid® (thalidomide) and its derivative Revlimid® (lenalidomide) – drug rescuing

- Original indication: Insomnia and morning sickness (shelved in the 1950's)
- Approved indications: Multiple myeloma (1999) and leprosy



•Retrovir® (AZT) – therapeutic switching / repositioning

- Original indication: Cancer (shelved in the 1960's)
  - Azidothymidine was first synthesized at the Michigan Cancer foundation in 1964 as part of a program directed toward the discovery of anticancer drugs. It gave negative results and attracted little further interest.
- Approved indication: AIDS (approved in 1987)

•Viagra® (Sildenafil) – drug repositioning

- Original indication: Angina, PAH
  - Phase I clinical trials under the direction of Ian Osterloh suggested the drug had little effect on angina
- Approved indication: Erectile dysfunction

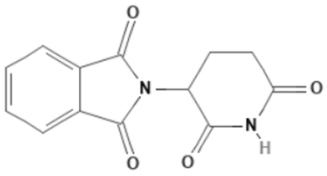
Case Study: thalidomide - history

- 1957: Originally marketed in Germany and UK as a sedative and targeted to pregnant women to treat morning sickness.
  - No regulatory approval required – marketed as “completely safe”
  - Worldwide >15,000 children – born to mothers who had taken it in the first trimester – suffered spinal defects and withdrawn from market in 1961 after having been sold in 46 countries.
  - Led to worldwide reforms of regulatory law around demonstration of efficacy and safety.
- 1964: First treatment of erythema nodosum laprosum (ENL) – complication of leprosy characterized by large, persistent, painful boils and inflammation so severe it often leads to blindness.
  - Celgene obtains approval in 1998 for Thalomid® for use in treating ENL.

Case Study: thalidomide - history

- 1994: Robert D'Amato, in Judah Folkman's lab, reported that thalidomide is an angiogenesis inhibitor.
    - Also explains, in part, the devastating effects in fetal limb development.
- 1997: First patient treated with thalidomide for multiple myeloma after having failed to respond to other treatments.
    - Leads to clinical study with 84 patients previously treated but refractory.
- 1998: Celgene acquires rights Children's Hospital method of use patent for treating cancer.
- 2006: FDA label approval for multiple myeloma.

Case Study: thalidomide – exclusivity strategy

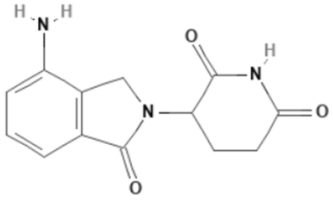


Thalomid (thalidomide)
Approved for ENL in 1998
Approved of MM in 2006

9 patents listed in Orange Book –
all directed to methods of segregating patients

Orphan drug designation: ENL, AIDS-related wasting and mycobacterial infections, Crohn's disease, others

Case Study: thalidomide – exclusivity strategy



Revimid / Revlimid (combination of lenalidomide and dexamethasone) - approved for MM in 2005

27 patents listed in Orange Book

- 4 patents directed to active ingredient, including composition of matter
- 5 patents directed to formulation
- 2026 expiry for crystal polymorph patent

Orphan drug designation: MALT lymphoma multiple myeloma, follicular lymphoma, mantle cell lymphoma, and myelodysplastic syndrome associated with isolated del(5q) chromosome abnormality

Players in the Drug Repurposing Space

- Repurposing Technology Companies
  - Biovista, Inc.
  - Thar Pharmaceuticals - owns Grunenthal
  - Insilico Medicine
  - Neurohealing Pharmaceuticals
  - Som Biotech - Orphan Drugs
- Large Pharma
  - Astrazeneca
  - Glaxosmithkline
- Academia and Research Institutes
  - Houston Methodist Research Institute
  - Johns Hopkins University
  - Michigan State University
  - Vanderbilt University

Inventor discloses…

I've shown that known Drug X:

•Has an activity on a target in a cell-based or in vitro assay.

•Demonstrates efficacy in an in vivo model.

Many questions need to be asked / discussed / strategized in order to determine best strategy to potentially realize value from the discovery / invention.

Evaluation is very different than if the drug were an NCE as it needs to consider:

•What type of repurposing is this?

•What type of exclusivity (patents and/or regulatory) applies?

Key Considerations - Scientific

Successful repurposing requires a deep understanding of various mechanisms and drug profile from:

- Understanding and reinventing the molecule (perhaps to a new molecule (prodrug) or combination of molecules), to
- Finding a new mechanism, to
- Understanding the formulation, to
- Figuring out the dosing, to
- Understanding the route of administration, to
- Understanding the new target

What can be done in the laboratory of the inventor(s)?
What funds are available to carry out key studies?

Key Considerations - Scientific

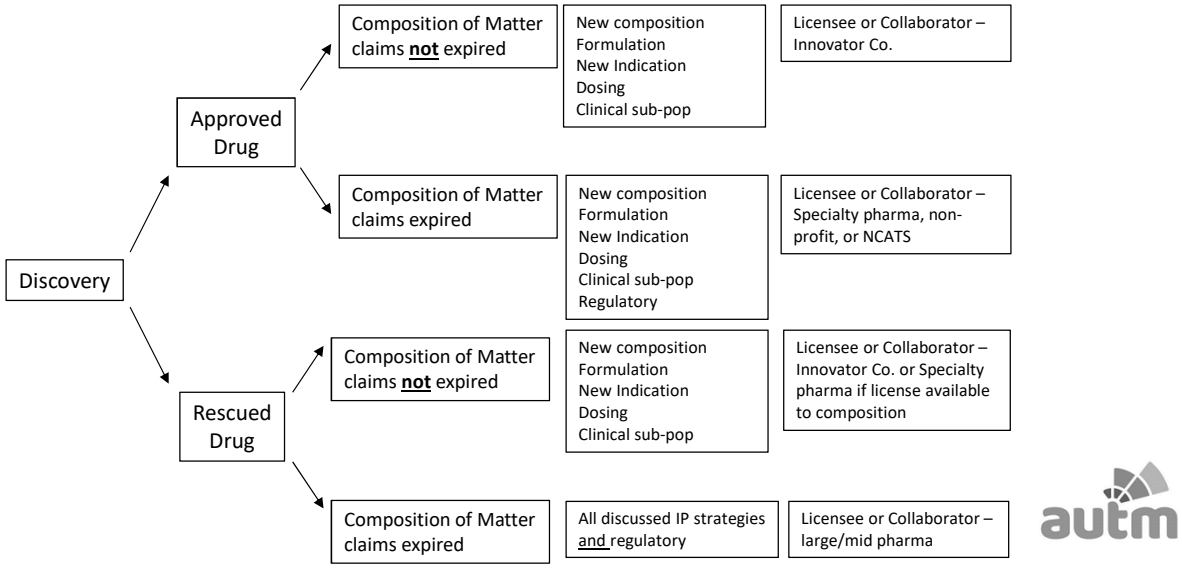
Are there any institutional technology platforms or skills that can be brought to bear?

- Formulation group in pharmaceutical sciences?
- Medicinal chemists with expertise in prodrug design?
- Clinicians with access to appropriate patient populations
  - Studies on existing tissue or sample banks
  - Prospective studies based on laboratory results (phenotype, genotype, mutations, etc.)

Strategies for Exclusivity – Patent

- More complex than patent strategy for an NCE.
- Requires greater dialogue between inventors and TTOs.
- Determine the type of repurposing and be conscious of the type of data that will help create value on the patent side.

Overview - Patent strategy approaches



Exclusivity strategy depends on type of repurposing: repositioning.

•**Repositioning** - if the known drug is already approved for clinical use in humans after achieving New Drug Application (NDA) approval.

- If approved – what jurisdiction(s)?
- On-Target Repositioning: pathway or target is the same as for the original indication (~80% of drug repositioning efforts have occurred through this route; most examples of this are “evergreening” strategies by pharma).
- Off-Target Repositioning: the mechanism of action, pathway or target is different from the original indication.
- Important parameter – is the drug generic or not?
  - Are there any composition of matter claims still within term?

Exclusivity strategy depends on type of repurposing: rescuing.

•**Rescuing** - if the first drug did not yet achieve NDA approval, so is not in commercial use.

- Failed to meet efficacy endpoints, but otherwise good safety profile.
- Safety issues at the doses required for the original indication.
- Different therapeutic approach supersedes original drug.
- Still important – are there existing patents, particularly composition of matter patents?

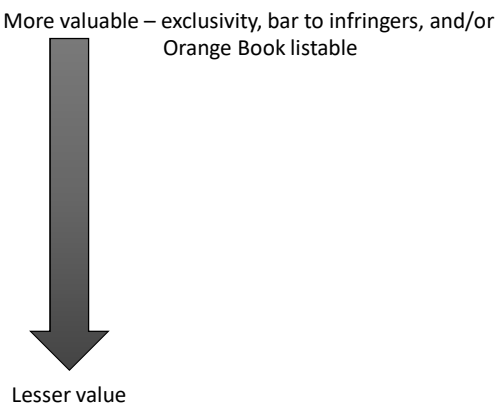
Value continuum – patent approaches for repurposed drugs

•Composition of matter
- Enantiomers
- Prodrug
- Polymorph
- Salt forms
- Drug combination

•Formulation

•Method of treatment
- Dosing Regimen (frequency and/or dose level)
- New clinical indication
- Combined with assay to segment clinical population

•Methods of manufacturing



Composition of Matter Patents – US, EP, JP

Opportunities	Challenges

• Patent protection may be available for a prodrug, polymorph, enantiomer or other salt form of an innovator drug or combination of APIs if there is evidence of surprising and/or unexpected results (U.S., EP and JP)
• Patent term extension may be available
  • Up to 5 years in the U.S. (plus up to 6 months for a pediatric extension)
  • Up to 5 years in EP (plus UIP to 6 months for a pediatric extension)
  • Up to 5 years in Japan (more than one patent can be extended)
	• If not yet expired, may need a license to the API patent from the innovator
	• Patentability may be tough in view of innovator patents (depending on disclosure relating to prodrugs, polymorphs, enantiomers, salts and combinations)
	• Can be designed around by competitors (particularly for prodrug, polymorph, enantiomer, salt form patents)

Formulation Patents – US, EP, JP

Opportunities	Challenges

• Patent protection may be available for a new formulation particularly when combined with a new use (U.S., EP and JP)
  • If API patent is not yel expired, innovator may be interested in licensing and/or collaboration
• Patent term extension may be available
  • Up to 5 years in the U.S. (plus up to 6 months for a pediatric extension)
  • Up to 5 years in EP (plus UIP to 6 months for a pediatric extension)
  • Up to 5 years in Japan (more than one patent can be extended)
	• May be tricky to get in terms of patentability if innovator filed formulation patents – may need evidence of surprising and unexpected results
	• If composition of matter patent is not yet expired, will likely need a license from the innovator
	• If composition of matter patent is expired, it may be easy for generics to design around your formulation

Method of Treatment – New indication

Opportunities	Challenges

• U.S.: Patent protection may be available for a new method of treatment/new use (new indication)
• EP and JP: Methods of treatment are not patentable
  • EP: Reformulate as EPC2000 type claims (Substance X for use in treating disease B.)
  • JP: Reformulate as second-medical use claims or Swiss-type claims (Use of substance X for the manufacture of a medicament for treating disease B)
• Patent term extension may be available
	• May be tricky to get in terms of patentability depending on disclosure in innovator's patent as well as prior art
	• If composition of matter patent is not yet expired, will likely need a license from the innovator
	• If innovator's composition of matter patent is expired, and the repurposing position is solely a new use of the API, preventing off-label use may be challenging (unless innovator's API never received FDA approval (e.g. was shelved))

Method of Treatment – Dosing Regimen / Clinical sub-population

Opportunities	Challenges
• Patent protection may be available for a new dosing regimen particularly when combined with a new use (mg/kg versus fixed weight dosing; dosing to avoid a food effect) or selection of a unique patient population (sub-group) for administration of a drug (U.S., EP and JP) • If API patent is not yet expired, innovator may be interested in licensing and/or collaboration • Patent term extension may be available	• If composition of matter patent is not yet expired, will likely need a license from the innovator • Watch out for inherency with claims to unique patient population (sub-group) • For dosing regimen patents, depending on how specific the regimen is, it may be easy for 3rd parties to design around the claims

Key Considerations – Regulatory - US

•If the drug to be repurposed is an already-approved drug, the requirement to conduct phase I and IIa clinical trials is likely to be significantly reduced

- Amount of safety data needed is determined by FDA on a **case-by-case basis** (depends on host of facts, indication, dosage, etc.)
  - Less safety information will be required if the repurposed dosage will be the same or less than the approved dosage
  - More safety information will be required if repurposed route of administration is different than approved dosage
  - Combination drugs may require bridging studies showing safety of drugs in combination

US FDA: 505(b)(2) pathway

•If repurposed drug was previously approved, then often can use a 505(b)(2) application process instead of a 505(b)(1) NDA application.

- Allows the applicant to rely on published studies and/or the FDA's safety and effectiveness findings from studies contained in the NDA to satisfy the "full reports" requirement under the Food, Drug & Cosmetic Act
- There will need to be a scientific or medical "bridge" between the product that is the subject of the 505(b)(2) application and the product that was the subject of the previously approved related NDA or was the subject of the studies in the public domain

•Other considerations for 505(b){2) applications:

- Patent listing in Orange Book is available and drug certification required
- 30 month stay is available, but no 180 day exclusivity

Changes available under a 505(b)(2) approach

•Types of changes to approved drugs for which a 505(b)(2) application can be submitted:

- Formulation
- Dosing regimen
- Active ingredient
- New molecular entity
- Combination product
- Indication
- Rx/OTC switch
- New device in a combination product

US Regulatory considerations – Rescued drug

•If the drug to be repurposed is **not** (i.e., a rescued drug) an already-approved drug, more extensive phase I and IIa clinical trial testing may be needed (compared to when there exists and already approved drug)

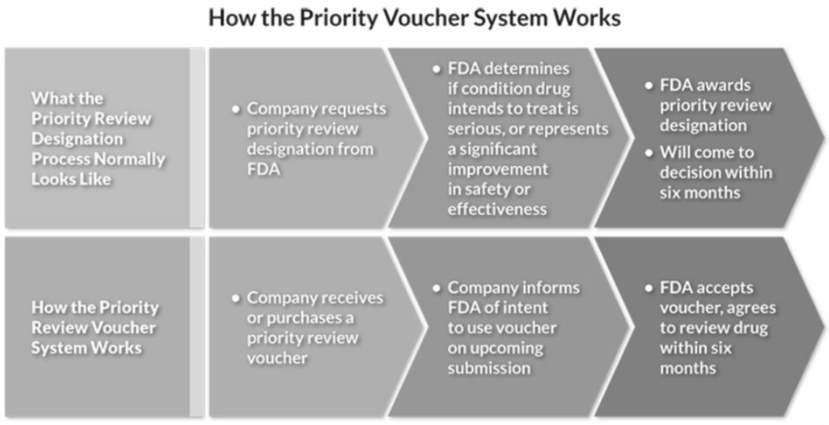
- May be able to rely on clinical studies conducted previously with the drug and published in the literature
  - If studies in literature are missing certain key information, FDA may require the study be repeated
    - Example: Published studies says suicidal ideation was evaluated but does not say how this metric was evaluated
- Various ways to incorporate safety studies
  - Maybe able to include in phase II or III efficacy studies
  - May depend on how most cost effective to conduct the safety studies

Summary - Regulatory Exclusivities Available in US

- Orphan Drug Exclusivity – 7 years
  - Diseases or conditions affecting fewer than 200,000 in the U.S.
  - Bars FDA from accepting an application for the same drug for the same orphan disease for 7 years.
- New Chemical Entity Exclusivity – 5 years
  - Chemical entity not previously approved by FDA (but can be approved elsewhere)
- Other Exclusivity – 3 years
  - Granted to drug when application contains reports of new clinical investigations essential for approval.
  - Data exclusivity
- Pediatric Exclusivity – 6 months

Key Considerations – Regulatory - US

Priority Review Voucher Program (PRV)



https://www.raps.org/regulatory-focus/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fdas-priority-review-vouchers

Overview – Priority voucher program

PRV Program

•Became law as part of the Food and Drug Administration Amendments Act (FDAAA) of 2007

- Under the law, a developer of a treatment for a neglected or rare pediatric disease or a material threat medical countermeasure receives a voucher for priority review from the FDA to be used with a product of its choice or sold to another developer
  - Priority review means that the FDA aims to render a decision in 6 months on a NDA or BLA (rather than 10 -12 months)

"Although FDA's goal is to take action on /he application within 6 months after /he 60 day filing period for en application involving a new molecular entity or within 6 months after the date of receipt of an application not involving a new molecular entity, this timeframe is not guaranteed."

Note that "take action" in this context means that FDA aims to complete its review of the filed applicauon and issue an approval or complete response letter within this limeframe; it does not mean that the application will be approved within this timeframe."

PRV Types Currently Available

•Three types of PRV

- Tropical Disease Priority Review Voucher
  - Examples: Tuberculosis, Malaria, Blinding trachoma, Buruli Ulcer, Cholera, Dengue/Dengue haemorrhagic fever, Dracunculiasis (guinea-worm disease), Fascioliasis, Filoviruses (cuevavirus, Marburg virus, and Ebola virus), Zika virus, etc. (20 total)
- Rare Pediatric Disease Priority Review Voucher
  - Disease is a serious or life-threatening disease in which the serious or life threatening manifestations primarily affect individuals aged from birth to 18 years
  - May or may not qualify for orphan drug designation (e.g., be enough for a rare pediatric disease designation but not likely enough for an orphan-drug designation
- Material Threat Medical Countermeasures Review Voucher

Examples - Business value of a PRV

Status of Existing Priority Review Vouchers		
Company	*Voucher Type*	*Status of Voucher*
Janssen	Tropical Disease	Successfully used to accelerate the approval of Tremfya (guselkumab) to treat plaque psoriasis.
BioMarin	Rare Pediatric Disease	Sold to Sanofi and Regeneron for $67 million. Used successfully to speed the approval of Praluent.
Knight	Tropical Disease	Sold to Gilead Sciences for $125 million. Gilead announced it had used the voucher in support of its NDA filing for its HIV drug Odefsey. FDA approved the drug in six months on 1 March 2016.
United Therapeutics	Rare Pediatric Disease	Sold to AbbVie for $350 million in August 2015. AbbVie has not disclosed how it plans to use the voucher.
Asklepion Pharma	Rare Pediatric Disease	Transfered to Retrophin under an existing agreement. Sold to Sanofi for $245 million in May 2015. In February 2016 Sanofi redeemed the voucher to support its NDA for a new type 2 diabetes drug.

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Examples - Business value of a PRV

Status of Existing Priority Review Vouchers		
Company	*Voucher Type*	*Status of Voucher*
Wellstat Therapeutics	Rare Pediatric Disease	Transferred to AstraZeneca under an existing agreement. Unused by AstraZeneca.
PaxVax Bermuda	Tropical Disease	Unused. Likely sold to Gilead for ~$200 million in 2016.
Alexion Pharmaceuticals	Rare Pediatric Disease	Used to speed the review of ALXN1210, which is a treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH)
Sarepta Therapeutics	Rare Pediatric Disease	Sold to Gilead for $125 million in February 2017. Used by Gilead to speed FDA's review of its new HIV treatment.
BioMarin	Rare Pediatric Disease	Sold to an undisclosed party for $125 million in November 2017.
Ultragenyx	Rare Pediatric Disease	Sold to Novartis for $130 million in December 2017. Used to speed the review of the MS drug BAF312 (siponimod).
Spark Therapeutics	Rare Pediatric Disease	Sold in April 2018 for $110 million to Jazz Therapeutics.
Ultragenyx	Rare Pediatric Disease	Sold to undisclosed party for $80.6 million.

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Questions?

- There are more resources and funding opportunities available for drug repurposing than ever before.
- Repurposed assets offer blockbuster potential with lower risks and costs to develop.
- Identifying the type of repurposing should be a first step in developing patent and commercialization strategies.
- Patent strategy for drug repurposing will depend upon the data available.
- Regulatory exclusivities can take the place of or supplement patent exclusivities.
- If a neglected or rare pediatric disease, the priority review vouchers may be available and are very valuable.