



# 2023 CDRC Annual Meeting

April 18 - 20



Critical Path Institute is supported by the Food and Drug Administration (FDA) of the Department of Health and Human Services (HHS) and is 55% funded by the FDA/HHS, totaling \$17,612,250, and 45% funded by non-government source(s), totaling \$14,203,111. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.



### Agenda



#### **CDRC Annual Meeting and Workshop Day 1: Tuesday April 18 Morning**

| <ol> <li>Introduction and welcome address: Rosie Lovett (NHS)</li> </ol> | 8:30 - 8:35   |
|--|---------------|
| 2. Paths to maximize use of existing drugs: Marco Schito (C-Path)        | 8:35 - 8:45   |
|  |               |
| Cochairs: Marco Schito and John Liddicoat                                |               |
| 1. Lightning talks introducing international programs                    |               |
| 1. Rosie Lovett (NHS)  | 8:45 - 8:50   |
| 2. Heather Stone (FDA)   | 8:50 - 8:55   |
| 3. Sundeep Agrawal (FDA)   | 8:55 - 9:00   |
| 4. Perdita Taylor Zapata (NICHD)   | 9:00 - 9:05   |
| 5. Sabine Grimm (REPO4EU)  | 9:05 - 9:10   |
| 6. Donald Lo (REMIDi4ALL)  | 9:10-9:15     |
| 7. Charlotte Asker-Hagelberg (Sweden - MPA)                              | 9:15 - 9:20   |
| 2. Questions/Answers   | 9:20-10:00    |
| 3. BREAK   | 10:00 - 10:30 |
|  |               |





#### **CDRC Annual Meeting and Workshop Day 1: Tuesday April 18 Morning**

#### Moderators: Rosie Lovett and Donald Lo

- 1. What projects is NHS program seeking, how do we search for them **Rosie Lovett** (NHS) 10:30 10:35
- 2. Design & plans for the REMEDi4ALL infrastructure & portfolio **Donald Lo** (REMEDi4ALL) 10:35 10:40
- 3. STAMP Perspective Charlotte Asker-Hagelberg (Sweden MPA)
- 4. BPCA Perspective **Perdita Taylor-Zapata** (NICHD)
- 5. Panel 1: Candidate Identification
  - 1. Charlotte Asker-Hagelberg (Sweden MPA)
  - 2. Perdita Taylor-Zapata (NICHD)
  - 3. Heather Stone (FDA)
  - 4. Sundeep Agrawal (FDA)
  - 5. Sabine Grimm (REPO4EU)
  - 6. Marjon Pasmooij (Netherlands MEB)

#### 6. LUNCH

12:00 - 1:00

10:40 - 10-45

10:45 - 10:50

10:50 - 12:00



#### Thanks to our sponsors



**x**Cures

#### Housekeeping items

• WiFi, breaks, posters, bathrooms

**Opening remarks** 

#### Lightning talks



## Rosie Lovett (NHS)

Teaching Old Drugs New Tricks: International Workshop for Publicly Funded Repurposing Programmes



April 18 2023, Arlington Virginia

#### Cure Drug Repurposing Collaboratory

#### Medicines Repurposing Programme, England

**REMEDi4ALL** 



FDA; National Institute of Child Health and Human Development

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#### Aims

Focusing on repurposing projects which do not have a commercial sponsor:

- Share information on international repurposing initiatives
- Discuss key challenges and potential solutions, focussing on:

   how to identify and prioritise candidate medicines for repurposing
   RCTs and licensing: funding and incentive mechanisms
- Establish an informal network
- Explore opportunities for more substantive collaboration



| 8.45  | Lightning introductions from 8 programmes, Q&A   |  |  |
|-------|--|--|--|
| 10.00 | Break  |  |  |
| 10.30 | Panel 1: Candidate identification  |  |  |
| 12.00 | Lunch  |  |  |
| 1.00  | Finance and intellectual property: Vikas Sukhatme, Żaneta<br>Zemła-Pacud, James Robinson, Savva Kerdemelidis |  |  |
| 2.20  | Break  |  |  |
| 2.50  | Panel 2: RCTs, licensing, trial funding  |  |  |
| 4.40  | Closed session with publicly funded programs   |  |  |



# How do you define drug repurposing?



- The investigation of existing approved drugs for new therapeutic purposes
  - $\circ$   $\,$  To maximize the effectiveness of our current arsenal of drugs  $\,$
  - Determine efficacy for a new disease/condition, dose, population but also to evaluate harm
  - What can we learn from our colleagues globally?

#### 1. Drugs that target shared pathways

- The biological target of the drug is same, but the disease is different
- Remdesivir (an RNA-dependent RNA polymerase originally for the treatment of HCV, then Ebola, that failed in a phase II clinical trial) has been approved for COVID-19

#### 2. Drugs that may be effective through off-target pathways

- Drugs act on new targets, out of the original scope, for the therapeutic indications.
- Aspirin has been traditionally used as NSAID in the treatment of various pain and inflammatory disorders.
- It also suppresses blood coagulation (clot formation) by inhibiting the normal functioning of platelets (antiplatelet drug).

## Optimal drug-disease utilization (ODDU)/









## A few examples of optimal drugdisease utilization



| Drug name    | Original indication  | New indication  | Date of<br>approval | Repurposing approach<br>used  | Comments on outcome of<br>repurposing  |
|--------------|----------------------|---|---------------------|---|--|
| Minoxidil    | Hypertension         | Hair loss   | 1988                | Retrospective clinical<br>analysis (identification of<br>hair growth as an<br>adverse effect) | US sales for minoxidil were\$600<br>million in 2020 (Questale minoxidil<br>sales report 2021)  |
| Thalidomide  | Morning sickness     | Erythema<br>nodosum leprosum<br>and multiple<br>myeloma | 1998 and<br>2006    | <u>Off-label usage</u> and pharmacological analysis   | Thalidomide derivatives have<br>achieved substantial clinical and<br>commercial success in multiple<br>myeloma                           |
| Fingolimod   | Transplant rejection | Multiple sclerosis                                      | 2010                | Pharmacological and<br>structural analysis  | First oral disease-modifying therapy<br>to be approved for MS. Global sales<br>for fingolimod (Gilenya) reached \$3.1<br>billion in 2017 |
| Ketoconazole | Fungal infections    | Cushing syndrome  | 2014                | Pharmacological analysis  | Approved by the EMA for Cushing syndrome in adults and adolescents above the age of 12 years   |

• There are many examples of generic drugs that can be repurposed but the pathway for regulatory approval have many barriers

# Probability of new indication exclusivity granted by FDA





Of the 197 new drugs that subsequently experienced generic entry, only 64 (32%) had at least one new indication added (1997-2020)

- Limited duration of exclusivity reduces the number of secondary indications significantly
- Much room for improvement for unlocking existing medicines' full therapeutic potential

Sahragardjoonegani et al. J of Pharm Policy and Pract 14, 3 (2021).

# On patent drugs: Challenges and opportunities



- Sponsor may be interested in label expansion from a financial perspective
   But not always...
- Estimated that 24% of the drugs that entered clinical trials were stopped for reasons unrelated to safety or efficacy
  - "Strategic business decisions" were the second-most common reason for companies to suspend development of experimental medicines, trailing only "a lack of efficacy"
- Typically, small biotech startups will take these chances but need access to patents and other relevant IP
- Large companies starting to engage
  - Takeda licensed one of its previously shelved assets, sapanisertib, to Calithera Biosciences, a small biotech based in San Francisco.
    - Calithera Biosciences folded on Jan 29, 2023
  - **Pfizer** spun out **SpringWorks Therapeutics** which assesses the potential for shelved assets to develop into new treatments for rare tumors and cancers.

# Do we need a label change for repurposing off patent generic drugs?



- Drug labels allow pharma companies to market the drug for the intended indications
  - Often result in new guidelines, updates formularies, addresses reimbursement issues
  - Provides prescribers high quality data to base treatment practices
- However, when was the last time a physician read a label?
- Without sponsor, there is no mechanism under the current paradigm to update drug labels especially for generics
  - $\circ$   $\,$  No incentives for drug developers
  - Generic drug manufacturers are ill equipped, lack resources, and are unable to act as a sponsor
  - Drug continues to be used off-label
  - $\circ$   $\,$  Some potential mechanisms exist to obtain a label supplement
    - ✓ Focus of this workshop

# Lack of sponsorship: Responsibilities (not exclusive)



- Financial
  - Protocol development
  - Trial funding and insurance
  - Drug manufacture (QA/QC, safety, active pharmaceutical ingredient (API) management)

#### • Site selection and management

- Site activation (clinical trial agreement, licences, approvals, site visits)
- Quality management system including protocol specific SOPs, training documentation, analyte QA/QC
- Data collection (IC, eligibility, missed visits, follow up, SAEs, study discontinuation...)
- Financial agreements, training staff, records retention...

#### Monitoring activities

- Monitoring, Safety, and Risk management plans
- Regulatory Authority interaction (21 CFR 312 for IND submission, notification....)
  - Intellectual property (IP) management at site level
  - Study Documents filing (Investigator Site File and Trial Master File)
  - Pharmacovigilance (PV) activities to comply with safety reporting obligations

## Lightning Talks





## Lightning Talks



- **1.Rosie Lovett (NHS)**
- 2.Heather Stone (FDA)
- **3.Sundeep Agrawal (FDA)**
- 4.Perdita Taylor Zapata (NICHD)
- **5.Sabine Grimm (REPO4EU)**
- 6.Donald Lo (REMIDi4ALL)
- 7.Charlotte Asker-Hagelberg (Sweden MPA)
- 8. Marjon Pasmooij (Netherlands)



We define "Drug Repurposing" as...

#### Use of an existing medicine, outside its current UK marketing authorisation

- In remit:
  - New indication, dose, treatment schedule, formulation
  - Generic, biosimilar, branded
- Out of remit: medicines not licensed for human use in the UK
- Example: anastrozole for preventing breast cancer in women at increased risk

# Medicines Repurposing Programme, England



#### Successes and challenges Medicines Repurposing Programme, England



National multi-agency support

Piloting regulatory pathway for generics

Portfolio expanding (slowly)

Stringent entry criteriahard to find suitable candidates

Will regulatory pathway be generalisable?

Small team, limited resources

## My goals for this meeting





### Definition CURE ID, USA



#### We define "Drug Repurposing" as...

**Drug repurposing** is the identification of potential novel uses of <u>existing (approved) drugs</u> typically we are referring to FDA-approved drugs sometimes includes those approved by other regulatory authorities

**Drug repositioning** is the term we use to describe the identification of potential novel uses of <u>unapproved drugs</u> that have been developed for another indication

#### Repurposing includes:

New ways of treating diseases,

New combinations of drugs that may be useful,

New dosing regimens and durations of therapy,

New populations that may benefit from existing treatments,

OR

Unapproved uses that **do not work or are harmful** to patients.

### CURE ID, USA



#### Successes and challenges CURE ID, USA

CDRC CRITICAL PATH INSTITUTE Challenging cases... New approaches

# More than 5,000 cases included in the platform

1<sup>st</sup> EHR data push

Potential for new uses (SPIND reporting)

fficulty getting cases from clinicians

Challenge of getting EHR data infrastructure built at institutions and data transferred to CURE ID

Large scope of interest with many sub-component pieces

### My goals for this meeting





## Project Renewal: United States FDA

## Successes and challenges

Project Renewal: U.S. Food and Drug Administration



Established repeatable, objective process for evaluation of potential updates

Engagement within FDA and with external stakeholders, including Industry

First approval of labeling supplement (Xeloda) based on Project Renewal review Long time horizon for each label (improving with experience)

Regulatory complexity (Initial framework established)

Time and Resources

## My Goals for this Meeting

Discuss

Project

Renewal

projects

experience so

inform similar

it may help

Learn about similar initiatives Share experiences and ideas with others to potentially facilitate our work

## NIH Best Pharmaceuticals for Children Act (BPCA) Clinical Program



#### Successes and challenges NIH BPCA Program



# Focused Legislations (BPCA, PREA, RACE)

NIH Program: 40 clinical studies 18 label changes

Recruitment of >12,000 patients Engagement with >120 clinical sites Special Populations Neonates Orphan Drug Designation

Limitations remain: Recruitment (sample size) Staffing Pipeline of experts Local logistics (IRB)

Kids are still are limited financial market (i.e. ROI)

### My goals for this meeting





### Definition

REPO4EU, Europe / global



A new use in a disease on a different ICD axis, even if the molecular target is the same (on-target repurposing) and/or the biological effect is the same but in a different organ context.
### REPO4EU, Europe / global



#### Successes and challenges REPO4EU, Europe / global



Expertise in all relevant fields covering the whole drug repurposing process up to PoC

Paradigm shift how to define diseases, i.e., not by organ or symptom, but by causal mechanism module

GMP-compliant repurposing at any dose with 2D/3D printing, also for different targets

Challenges to drug repurposing, e.g., patenting, funding, clinical trial sites, regulatory

Long-standing REPO-TRIAL team, but HTA, regulatory, advanced trial designers and statisticians new

Clinical validation of superiority of approach is key (first results in 2023: PAD, stroke, HFpEF)

### My goals for this meeting







### **Definition** REMEDi4ALL, Europe & UK



#### We define "Drug Repurposing" as...

Widest possible net, including:

- a) Generics
- b) On-patent drugs
- c) Investigational stage, on- or off-patent
- d) Off-patent, off-market
- e) Off-label usage that is already standard-of-care

### REMEDi4ALL, Europe and UK



#### Successes and challenges REMEDi4ALL, Europe and UK

CDRC CRITICAL PATH INSTITUTE Challenging cases... New approaches

European Union funding validates importance of goals

Consortium launched, hooray, already 7mo old!

Broad vision to improve entire drug repurposing ecosystem

Basic research and drug development are still very different worlds

Much critical data for original approvals remain proprietary

Funding: repurposing is still not "sexy"

### Our goals for this meeting





#### The European repurposing pilot Sweden - MPA



### Successes and challenges, to be evaluated....

#### The EMA and HMA pilot

The European Commission's STAMP meeting initiated discussions

Multistakeholder engagement

Surge from non-profit stakeholders and academia Interest in pilot according to project applications received The level of evidence that should be generated and availability of data e.g. IP, preclinical

Clinical trials Study design, funding

Weak regulatory tools if no MAH willing

#### My goals for this meeting Sweden - MPA





### Drug Rediscovery Programme, The Netherlands





## 19 funded projects, results coming available from 2022 onwards

## Including pre-grant advice from the MEB

Jusiness case (return of investment)

## Willingness of investigator to pursue registration

### My goals for this meeting





### **Question & Answer**





Break





### Drug Rediscovery Programme, The Netherlands

- Sixth Round Drug Rediscovery Programme (ZonMW Dunja Huijbers)
- In remit:
  - Efficacy and/or dose optimalisation of existing medicine (out of patent) for new indication
  - Clinical (proof of concept or validation study) not preclinical research this round
  - Maximum duration of 10 years, 800.000
- Out of remit:
  - Medicines not licensed for human use in the NL
- Condition:
  - Medicine should be made available for patients for affordable price

### Drug Rediscovery Programme, The Netherlands

| Rediscovery Round | Project Ideas | Full proposal | Funded projects | Involvement MEB |
|-------------------|---------------|---------------|-----------------|-----------------|
| RR1 (2016 - 2017) | 23            | 10            | 4               | Ν               |
| RR2 (2017- 2018)  | 17            | 12            | 4               | Υ               |
| RR3 (2018 - 2019) | 29            | 13            | 3               | Y               |
| RR4 (2019 -2020)  | 22            | 13            | 4               | Y               |
| RR5 (2021- 2022)  | 35            | 12            | 4               | Y               |
| RR6 (2022 – 2023) | 17            | 8             | NTB             | Y               |
| Total             | 143           | 68            | 19 (13%)        |                 |

### Drug Rediscovery Programme, The Netherlands

• 1st rediscovery round project finished in 2022.

Follow-up on results in clinical guideline or registration for new indication (Q3 2023).

Results not yet incorporated in clinical guideline. Investigator is not aiming to go for registration for new indication (rare disease). Product can be prescribed off-label.

 2nd and 3rd project finished in Q1 2023, from which one had contact with MEB. 3rd project likely not sufficient data to go for scientific advice at MEB.

### Collaboration ZonMW - MEB

- MEB assesses selected proposals in the first round, this opinion is taking into account in which proposals are granted
- This advice has to be taken into account by the Applicant for the second round of the call
- Agency recently agreed for additional 4 years
- Previously for free, from 2022 payment from ZonMW to MEB

### Successes and challenges

Drug Discovery Programme, the Netherlands

19 funded projects, results coming available from 2022 onwards

Including pre-grant advice from the MEB

Jusiness case (return of investment)

Willingness of investigator to pursue registration





# What projects is NHS program seeking, how do we search for them?

### What is NHS programme looking for?



#### Summary eligibility criteria

- Repurposed use outside current licence: new indication, dose, formulation
- ✓ Evidence of safety and efficacy, ideally phase 2 trial
- ✓ As good or better than standard care
- ✓ Support from patients or clinicians
- $\checkmark$  Not already widely used
- ✓ Has UK or GB licence for human use



#### NHS candidate identification All conditions and populations





#### **Assess eligibility**

### NHS horizon scanning





### NHS horizon scanning



National Institute for Health and Care Research Innovation Observatory

| Inclusion criteria   | Exclusion criteria  |
|--|---|
| <ul> <li>Medicine type</li> <li>Used outside its existing licensed indication</li> <li>Generics, biosimilars, reformulations and on-patent</li> <li>Monotherapy or in combination</li> </ul> | <ul> <li>Unlicensed for any indication in the UK</li> </ul> |
| <ul> <li>Trial locations</li> <li>Study site in UK, EU, USA, Australia or Canada</li> </ul>  | <ul> <li>Single-site trials</li> </ul>                      |
| <ul> <li>Trial sponsorship</li> <li>Non-commercial, i.e. Investigator-Initiated Trials</li> </ul>  | <ul> <li>Commercial sponsor</li> </ul>                      |
| <ul> <li>Primary completion date</li> <li>Generally 12-15 months ago (quarterly readouts)</li> </ul>   |   |

### NHS horizon scanning: first year



- Identified 180 trials
- Over half ineligible: terminated, negative results, under-powered, medicine already part of standard care
- Monitoring 69 trials
  - $\circ$  Few results yet despite passing primary completion date: delayed by COVID?
  - $\odot$  Few researchers respond pre publication

### NHS horizon scanning: first year







### Questions

- Are other programs looking for similar medicines, or is their focus earlier in the development pathway?
- How do other programs identify candidate medicines?
- For programs with a condition/population focus: how was this chosen?
- How do others use real-world evidence of safety and efficacy?
- Can we draw on wider evidence sources: drug-target interactions, preclinical data, real-world data, safety data etc?



# Design and plans for the REMEDi4ALL infrastructure and portfolio -



# Designs and plans for the REMEDi4ALL infrastructure and portfolio





European infrastructure for translational medicine

Headquartered in Amsterdam The Netherlands

### Our vision



An EU research and innovation **ecosystem** that facilitates fast, cost-effective and patient-centric development and implementation of **repurposed medicines**, meeting high unmet medical needs in any disease area

# = floating all boats for drug repurposing

SAIL Amsterdam, 2016

### Why now, why here, why us?





- Huge interest and activity in repurposing
- But current ecosystem in Europe very fragmented
- No single entity can do it all



- REMEDi4ALL and REPO4EU
- EU stimulus
- Efficient and accessible eco-system
# Many of the 7000+ disorders with known molecular bases could potentially be addressed by drug repurposing





# ...but every time seems like reinventing the wheel.



Early experiments in transportation

Two Operational Goals





Build a complete, visible and accessible value chain for patient-centric DR



Create a think-tank that develops and advances DR policy

First part is the science side...



# But many challenges ahead before regulatory clearance to test in a clinical trial



### Key IND/CTA-directed activities that still may be required for repurposing of an even an approved and off-patent drug

- **DMPK:** Evaluation of functional activity, potency, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy
- Biomarker development
- Definition and optimization of dose and schedule for *in vivo* activity
- Development and implementation of pharmacological assays
- Chemical and biologics process research and development
- **Manufacturing** of bulk substance (GMP and non-GMP)

- Development of suitable **formulations**
- Development of analytical methods
- Production and stability studies of dosage forms
- Range-finding initial toxicity
- Investigational New Drug (IND)-directed toxicology, with correlative pharmacokinetics and histopathology
- Planning of clinical trials (Phase 1 and/or Phase 2)
- Regulatory and IND filing support
- Natural history and patient-finding studies







### A self-sustaining infrastructure and ecosystem for drug repurposing



\* \* \* \* \* \* \*

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442.

remedi4all.org #R4ALL #REMEDi4ALL



### **STAMP** Perspective

Date April 18, 2023

# The European repurposing pilot - candidate selection

#### **Charlotte Asker Hagelberg**





## The EU project application form - open to Champions



A Champion can be, for example, an entity or a person from an academic unit/charity or patient organisations/learned society/research funder or payer (generally seen as not-for-profit organisations).



The Champion should be able to foster a new indication to an existing "off-protection" product



The HMA and EMA regulatory networks are operative



Application by a form available at EMA website (12 items)



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#### $Repurposing \cdot pilot \cdot project \cdot for \cdot authorised \cdot medicines \P$

#### Submission · Form · ¶

 $(To \cdot be \cdot submitted \cdot \underline{to:} \cdot see \cdot Annex \cdot to \cdot the \cdot Q & A \cdot on \cdot repurposing \cdot pilot \cdot project - \cdot of \cdot note \cdot for \cdot submission \cdot to \cdot EMA: \cdot please \cdot use \cdot \underline{Eudralink}) \\ \P$ 

| Active-substance(s)¤   | ×   | × |  |
|--|---|---|--|
| Provide-the-name(s)-of-the-active-substance(s  | ;)·that·are·the·subject·of·repurposing¤   | × |  |
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| Champion <sup>B</sup> ×  | Provide-the-name-of-the-Champion×   | × |  |
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| New·proposed·condition·or·indication¤  | Describe¤   | × |  |
| Is·the·proposed·new·condition/indication·for·<br>the·authorised·active·substance·distinct·to·<br>the·currently·authorised·indication(s)·listed·<br>in·section·4.1·of·authorised·medicinal·<br>product(s)·in·the·EEA? | Yes/No¤   | × |  |
| Do·you·hold·an·orphan·designation·for·the·<br>proposed·repurposing·project?¤   | Yes/No¤   | × |  |

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### Eligibility for "free" SA within the EU pilot - if not rare disease





## **Results of screening**

Ca 30 projects were screened by EMA + NCAs

More than10 have been selected as eligible (EMA+ NCA, matter of resource)

New indications in different therapeutic areas, common and orphan conditions



## **Examples of therapeutic areas**



Cardiology



Psychiatry



```
Endocrinology
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Haematology



# **Status: Scientific Advice Entry Phase**

#### Advice is performed by standard procedures for the respective competent authority in EU member state.

#### **Experiences before Scientific Advice (SA):**

- Many pre-meetings needed before formal SA can take place:
  - ensure enough background information
  - formulation of questions to the Scientific Advice Working Party (SAWP)
- Champions:
  - Challenge for Champion to find time and navigate the procedural requirements for the SA, delay in initiating the SA procedure
  - Champions may lose momentum to continue
  - Some Champions must do the preparatory work on their free time outside clinical practise
  - Champions can sometimes benefit from pairing up with other bodies, e.g. patient organisations
  - Need technical support for submission in the database
- Regulators:
  - Good to gather Champions to collective meetings to inform on the process, challenges, answer general questions etc.
  - Pre-training of the Champions before engaging in pre-submission meeting (MPA)
  - Challenge to determine the level of evidence required, some questions complex, require several rounds of SA (MPA)
  - Some full SA already delivered and in one of the projects a company is active (AEMPS)



# Thank you!







#### Moderators: Rosie Lovett and Donald Lo

Introductions:

- What projects is NHS program seeking Rosie Lovett (NHS)
- Design and plans for the REMEDi4ALL infrastructure and portfolio Donald Lo (REMEDi4ALL)
- EMA pilot Charlotte Asker-Hagelberg (Sweden MPA)

#### Panel 1

- 1. Heather Stone (FDA)
- 2. Sundeep Agrawal (FDA)
- 3. Sabine Grimm (REPO4EU)
- 4. Marjon Pasmooij (Netherlands MEB)
- 5. Charlotte Asker-Hagelberg (Sweden MPA)
- 6. Perdita Taylor-Zapata (NICHD)

**10.30-11.00 First key question (discussion facilitated by Rosie):** Are programmes pro-actively searching for repurposed medicines at a certain point in the development pathway, and then deciding whether to adopt into their workstream? If so, how are programmes doing this? Any duplication or synergies?

Perdita Taylor-Zapata, please kick off the discussion by talking about how the BPCA identifies priority topics and if/how your approach to topic identification has changed over the years.



### **BPCA** Perspective

# 11.00-11.30 Second key question (discussion facilitated by Don):

What are the key barriers – either perceived or real – which make it difficult to start or to progress a repurposing project? Gap analysis – what support is available and how could it be better coordinated?

## Real and perceived barriers to drug repurposing...



Basic Research

development

Clinical trials

approvals

reimbursemen

## Lunch





## Agenda



1:40 - 2:00

2:00 - 2:20

### **CDRC Annual Meeting and Workshop Day 1: Tuesday April 18 Afternoon**

#### Cochairs: Marco Schito and David Simon

- Unleashing the Potential of Financial Orphans: Blueprint for a National Initiative –
  Vikas Sukhatme (Emory Morningside Center for Innovative and Affordable Medicine) 1:00 1:20
- Changes in European IP and regulatory system for medicines: A first swing at a drug repurposing framework – Żaneta Zemła-Pacud (Polish Academy of Sciences)
   1:20 – 1:40
- An Innovation Surcharge to Fund the Repurposing of Generic Drugs James Robinson (UC Berkeley)
- Using Interventional Pharmacoeconomics and Advance Market Commitments to Repurpose Generic Drugs with Cost Savings – Savva Kerdemelidis and Jason Cross (Crowd Funded Cures)
- 5. Break

Vikas Sukhatme - Emory Morningside Center for Innovative and Affordable Medicine



# Unleashing the Potential of Financial Orphans: Blueprint for a National Initiative



### Unleashing the Potential of Financial Orphans: Blueprint for a National Initiative

Vikas P. Sukhatme MD ScD and Vidula V. Sukhatme MS

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## Disclosures (VPS)

- Aggamin co-founder (preeclampsia therapeutics)
- BERG SAB (Al/pharma company)

Immunotherapy for cancer: amazing story but far from perfect.... a typical case

Immunotherapy for cancer: amazing story but far from perfect.... a typical case

Can we do better?

Can we do better **now**?

Can we do better **now** and with **inexpensive treatments**?

Possibly yes, take a look.

# Histamine 1 blocker to improve efficacy of PD-1 blockade in cancer



The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1 Li et al., 2022, Cancer Cell 40, 36–52

## Magnesium and T cell function

A role for Mg on cytotoxic T cell activity. Mg deficient diets accelerate metastases and show impaired response to influenza virus. LFA-1 is an integrin involved in cytotoxic T cell killing and in cell extravasation.

Magnesium sensing via LFA-1 regulates CD8<sup>+</sup> T cell effector function Lötscher et al., Cell *185*, 585-602; 2022



SAKK16/14 Trial - Durvalumab in NSCLC

## Pantothenic acid (vitamin B5) and responses



- High Pantothenic Acid
- Intermediate Pantothenic Acid
- Low Pantothenic Acid

(Pre-treatment tertiles; 14 patients per group; total 42 patients with melanoma)

St. Paul et al., 2021, Cell Metabolism 33, 2415–2427



Patients

## Commonalities in these examples?



No IP!



No significant money to be made; ideas will typically languish!

## The Problem

There are still many unmet medical needs. Treatments (when they exist) are:



AND new drug development takes 5-10 years, costs >\$1 billion, and has a high failure rate.
## A Solution: Focus on Financial Orphans

### **Financial Orphans**

Ideas not being pursued by the forprofit sector due to inadequate financial incentive

- No IP or IP difficult to enforce
- Market size
- Reimbursement potential
- Chance of successful clinical trials outcome

### HEALTH AFFAIRS FOREFRONT

RELATED TOPICS:

PHARMACEUTICALS | DISEASES | PATENTS | COSTS AND SPENDING | PHARMACEUTICAL COMPANIES | CANCER PATIENTS | MARKETS | CLINICAL TRIALS | PRESCRIPTION DRUG COSTS | NONPROFIT STATUS

## Financial Orphan Therapies Looking For Adoption

Vikas Sukhatme, Kathy Fang, Andrew Lo, Vidula Sukhatme

MARCH 6, 2014

10.1377/forefront.20140306.037370

## Financial Orphan Classes and Advantages



## Clinical Development Contrast

## **New Drugs**

Extensive preclinical data packet and adequate estimated ROI



Pharma pursues and recoups investment

## **Financial Orphans**

Promising but limited pre-clinical data, some human data, (retrospective, case reports, phase I/II studies) but insufficient financial ROI



Non-profits, government could pursue

## Clinical Development Contrast (contd)

|                     | Trials/Study Site  | e Protocol                | Funder  | Cost                                   | Access   | Data packet  | Goal   |
|---------------------|--|---------------------------|---|--|--|--|--|
| NEW DRUG            | Phases I,II,<br>III/<br>AMCs for<br>testing  | Drug<br>company<br>writes | Corporate<br>~\$70B for R<br>and D/year           | Industry pays<br>top \$ per<br>patient | Cannot<br>prescribe<br>prior to FDA<br>approval<br>except for<br>compassion<br>ate use | Extensive<br>pre-clinical<br>data with<br>optimized<br>drug;<br>human<br>safety<br>unknown         | FDA approval   |
| FINANCIAL<br>ORPHAN | Possibly skip<br>Phase I or II/<br>Community<br>studies to<br>speed impact<br>(AMCs for<br>safety,<br>feasibility and<br>correlatives) | Investigator<br>in charge | Non-profit,<br>government<br>Propose<br>\$1B/year | Modest<br>\$/patient                   | Can offer as<br>part of a<br>trial or as<br>off-label<br>treatment                     | Less extensive<br>preclinical<br>packet (dirty<br>drug) but<br>human safety<br>data often<br>known | Practice<br>guideline<br>change (and<br>label change in<br>countries<br>where off-<br>label use is<br>illegal) |

## Create a National Agency to Address Unique Features of Financial Orphan Clinical Development





IFOT would oversee and fund:

- financial orphan discovery effort
- clinical research infrastructure



IFOT would be very much like pharma except that **patient impact not ROI**, would **drive treatment** selection

### Institute for Financial Orphan Therapeutics (IFOT)



**Goal:** generate sufficiently strong clinical evidence to **change practice guidelines** 

## IFOT: Funded as a New FFRDC?

### IFOT could be a new Federally Funded Research and Development Center (FFRDC)



## IFOT: Other Funding Options



Incorporate within an existing federal entity by increasing budget



Establish a "Patient Benefit Fund" with new taxes



Develop novel "financial engineering" models



Engage foundations/charities



Pharma/biotech funding



Insurers (CMS), selfinsured healthcare systems



A public benefit corporation

## **IFOT Functions**



*IV. Ensure Treatment Access at a Reasonable Price*  III. Advocacy & Education



# I. Idea Generation & Prioritization

## I. Idea Generation & Prioritization

### Identifying Promising Candidates:



### Criteria for Candidate Prioritization/Advancement to Clinical Studies:



## Candidate Prioritization Scheme/Advancement to Clinical Trials

## Scientific Criteria

- Scientific/clinical data on efficacy and toxicity
- Magnitude of anticipated patient benefit
- Time to study completion
- Could study change SOC?
- Likelihood of IND application exemption
- Is there a critical path to clinical development?

## Non-Scientific Criteria

- Feasibility in AHC or in community setting
- Cost and funding availability
- Uniqueness of intervention
- Access to intervention
- Unmet needs assessment



# II. Design & Oversight of Clinical Studies

## II. Design of Clinical Studies: Trials



# Why Target the Community for IFOT Clinical Studies?



More eligible patients: quicker impact



Toxicity profile for repurposed drugs is well-established



Community patients don't have easy access to trials



Data will capture realworld diversity



Drugs for repurposing are readily available and familiar to MDs



Less competition with pharma-sponsored studies

## II. Design of Clinical Studies: Treatments Coupled to Registries

A unique opportunity for financial orphans: offer off-label treatments, not as part of a clinical trial, but with outcome tracking

# REGISTRY

- Patient perspective:
  - For those with no time to wait for trials
  - Easy access: community MDs engaged
  - Real-time data analysis
- MD
  - Minimize regulatory and administrative burden
  - Off-label use is legal with some medical evidence
- Other
  - Less expensive than trials and more rapid impact
  - Data might give early efficacy signal to be assessed in trials

## II. Challenges and Mitigation Strategies

### **Clinical Trials**

- Competition with pharma for patients
- Costly
- Funding for MD reimbursement
- Few patients in one AMC
  - Mitigation Strategy: FORM NETWORK
- May be available to only a few patients
  - Mitigation Strategy: EXECUTE IN THE COMMUNITY
- Lengthy time for study approval
  - Mitigation Strategy: USE A CENTRAL IRB
- Feasibility or difficulty due to FDA IND requirements
- Need community patients to have impact
- Legal liability
  - Mitigation Strategy: INSURANCE COVERAGE

### Treatments (off-label) with Registries

- Will we learn anything?
  - YES, IF REGISTRY IS SET UP
- Liability concerns and reputational risk
  - Mitigation Strategy: INFORMED CONSENT; COMMITTEE VETTING OF TREATMENTS; REAL-TIME ANALYSIS OF OUTCOMES WITH TRANSPARENT REPORTING; COULD ADD INTERVENTION TO MALPRACTICE COVERAGE
- Who in the clinical workflow prescribes interventions?
- MD education on treatment
  - Mitigation Strategy: MAKE A PROTOCOL AVAILABLE AS IF IN A TRIAL
- Funding for interventions and MD time not covered by insurance? Optics of patient paying?
- Funding for additional tests and outcomes assessment not part of SOC?
- Peer concerns
  - Mitigation Strategy: VETTING OF TREATMENT
    PROTOCOL BY A CENTRAL IRB; REAL-TIME OUTCOMES

# II. Oversight of Clinical Studies

# **IFOT** would be the **funder** and the **sponsor** of clinical studies.



### IFOT Oversight Activities

- Identify PIs and sites for studies
- All aspects of study design and protocol development (including statistical support)
- Work with PIs to obtain IRB approval, especially if an external IRB is being used
- Help file IND, if needed
- Support development of specific assays in a CLIA/CAP environment
- Develop/oversee web-based tools to consent. enroll & randomize patients
- Tools to capture, extract, and mine EHR data and patient outcomes
- Develop relationships; negotiate contracts and MOUs
- Establish CRO relationships to implement activities when needed.



# III. Advocacy & Education

## III. Advocacy & Education







Engage with FDA to simplify processes





# IV. Ensure Treatment Access at a Reasonable Price

## IV. Ensure Treatment Access at a Reasonable Price



If positive data on a particular financial orphan emerges, IFOT would Engage with the private sector to ensure that enough of the treatment is available to satisfy needs for the new indication

Ensure that there is no increase in price

## Leverage

### Activities of IFOT could be leveraged in many ways, including:



Pharma could use the "railroad tracks" to conduct studies



Pharma could benefit from early access to clinical outcomes data



Pharma could use the database to identify drugs that could be chemically modified or reformulated



Use caregiver network to rapidly gather data on interventions approved as an EUA in a national emergency, such as a pandemic

## Related/Complementary Work



# **Morningside Center Activities**

Database of "financial orphan" opportunities

We are creating a database for patients, physicians and investigators that provide information about potential interventions by disease and clinical stage with a singular focus on financial orphans. Our initial disease focus is cancer. Clinical impact

We generate ideas, identify potential investigators, design and write protocols and fund studies.

We share information about the potential of repurposing drugs and other financial orphans through conferences and other educational opportunities. We are involved with various organizations who advocate for better treatment options for patients. We are developing a detailed national blueprint for unleashing the full potential of financial orphans.

& Partnership

Advocacy, Education,

## Morningside Center Team



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Independent Contractor, Morningside Center Thank you



# Changes in European IP and regulatory system for medicines: A first swing at a drug repurposing framework

Changes in European IP and regulatory system for medicines: A first swing at a drug repurposing framework

Dr Żaneta Zemła-Pacud Insititute of Law Studies, Polish Academy of Sciences



### Coming changes in European IP & regulatory framework – an overview



## **Regulatory Exclusivities now:**

INNOVATIVE MEDICINES PEDIATRIC DRUGS authorised under PUMA

exclusivity periods divided into :

8 years of data exclusivity

2 years of market exclusivity

+ 1 year of market exclusivity if a new indication with a significant clinical benefit has been authorised

Directive 2001/83 Regulation 1901/2006 Regulation 1901/2006

### **ORPHAN MEDICINES**

= used in rare diseases, occurring in less than 5 for 10.000 people in the EU

10 years of data and market exclusivity

A broad scope of exclusivity, covering the same and similar products for the same orphan indication

### PAEDIATRIC REWARDS

6-month extension of SPC 2-year extension of orphan exclusivity

*Regulation* 1901/2006

Regulation 141/2000

## The longest-lasting form of protection of reference products

- 32% SPCs
- 19% paediatric extension of SPC
- 31% market exclusivity
- 11% patents
- 5% orphan exclusivities
- 2% paediatric extension of orphan exclusivity

During an SPC extension an average drug generated an additional 220 billion Euro

Mechanisms for the early generic entrance:

- SPC stockpiling waiver
- Separation of data and market exclusivity



https://www.iqvia.com/insights/the-iqvia-institute/reports/protection-expiry-and-journey-into-the-market

### Regulatory exclusivities: what changes are being considered?

### **INNOVATIVE & PEDIATRIC MEDICINES**

6 years of data exclusivity followed by 2 years of market exclusivity

and conditional periods + 2 years of DE if a product is marketed in all EU countries within 2 years of marketing authorisation and if continuous supply is ensured + 1 year of DE for products that address unmet needs

+ 6 months of DE for comparative studies

### **ORPHAN MEDICINES**

Data and market exclusivity variable in duration

8 years for products addressing High Unmet Medical Needs

6 years for innovative products

### 5 years for others

Extension of exclusivity will be possible for medicines meeting HUMN and innovative (new active substances), provided availability in all (relevant) Member States.

#### PAEDIATRIC MEDICINES

The existing 6-month extension of SPCs maintained

TRANSFERABLE EXCLUSIVITY VOUCHERS (TEV)

An incentive for new antibiotics,

1-year extension of a relevant period of market exclusivity (not the SPC term)

transferable to another company within 2 years

### Revision of the pharmaceutical regulation

### LEITMOTIFS:

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- MEETING UNMET MEDICAL NEEDS
- ANITIBIOTICS
- ENSURING EQUAL SUPPLY OF MEDICINES
- SHORTENING OF MA PROCEDURES
- FLEXIBILITY: CONDITIONALITY & MODALITIES
- LACKING HARMONISATION OF PRICING & REIMBURSEMENT

- THE MOST SIGNIFICANT REFORM TO THE HEALTHCARE REGULATORY SYSTEM IN 20 YEARS.
- FAR-REACHING SOCIAL, ECONOMIC AND LEGAL IMPACT

## The first swing at a drug repurposing framework

Scientific opinion on data submitted from not-for-profit entities for repurposing of authorised medicinal products

1. A '<u>not-for-profit entity</u>' may at any time submit to the Agency or to a competent authority of the Member State <u>substantive pre-clinical or</u> <u>clinical evidence</u> for a new indication for medicinal products authorised under this Regulation or for medicinal products <u>authorised in more</u> <u>than one Member State</u>.

The Agency may, at the request of a MS, the EC, or on its own initiative and on the basis of all available evidence make <u>a scientific evaluation</u> <u>of the benefit-risk</u> of the use of a medicinal product with a new therapeutic indication that concerns <u>an unmet medical need</u> which is <u>of</u> <u>major interest from the point of view of public health</u> in particular from the viewpoint of therapeutic innovation.

The opinion of the Agency shall be made publicly available (...)

2. In cases where the opinion is favourable, MAs of the medicinal products concerned <u>shall submit a variation to update the product</u> <u>information</u> with the new therapeutic indication or shall demonstrate that the conclusion of the opinion is not applicable to their medicinal product.

(An unofficial version of a new provision likely to be part of the EC proposal)

### Clinical Trial Data Transparency

### The CTIS has been operational since January 2023

The new Clinical Trials Regulation (EU) No 536/2014 (CTR) and introduction of the Clinical Trials Information System (CTIS) aim at more transparency and better access to clinical trial results, facilitating AI-driven drug repurposing.

**Benefits:** All clinical trials must be made public (also the unsuccessful ones), starting from Phase I Potentially facilitating secondary data analysis.

Drawbacks: Unclear system of redactions (for commercially confidential information) and deferrals (up to 7 years), the tendency to grant maximum periods of deferrals with no flexibility Lacking guidelines for Member States – risk of divergent domestic decisions Not easy-searchable format of disclosed data – no raw Individual Patient Data

## **Ongoing IP changes**

- The Unitary Patent System starts its operation in June 2023:
- European patents with unitary effect will exist in almost the whole EU, without Spain, Poland, Croatia and the UK

- the Unified Patent Court will have jurisdiction over unitary patents and classical European Patents. not entirely harmonized substantive patent law,

- transitional period of 7 years; possibility of opt-out and bringing EPs disputes to domestic courts

- Plans to introduce unitary SPCs
- Harmonisation of the Bolar exemption to cover third persons' activities?

**Conducting the necessary studies and trials** to meet the requirements of generic authorisation and the **consequential practical requirements** shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products. (Article 6 of directive 2001/83)
#### **Ongoing IP changes**

• Provisional patent applications – existing in Portugal, Austria, and France; legislation pending in Spain and Poland

#### • Sufficiency of disclosure for new therapeutical indications

According to a recent decision G2/21 of the EBoA, "In order to meet the requirement that the disclosure of the invention be sufficiently clear and complete for it to be carried out by the person skilled in the art, **the proof of a claimed therapeutic effect has to be provided in the application as filed**, in particular, if, in the absence of experimental data in the application as filed, it would not be credible to the skilled person that the therapeutic effect is achieved. A lack in this respect cannot be remedied by post-published evidence".

#### In search of ideas and recommendations

- Remaining problems: lack of sufficient incentives for investing in R&D leading to generic drug repurposing
- Even genuinely innovative and highly sought repurposed medicines cannot be introduced to the market during the existing patent protection

A remedy for consideration:

- statutory licence for new indications meeting hitherto unmet medical needs,
- relevant provisions could be introduced to the directive 2001/83
- EMA's crucial role: assessing whether a further therapeutic indication fulfils the criterion of UNM
- A high and easily verifiable threshold incremental changes would not lead to patent limitation
- EMA's opinion would be decisive for the self-implementation of the licence
- Should the new therapeutic indication be patented, in order to safeguard the interests of the patent holder, the statutory licence could be combined with a cross-license to the patent holder.

## Thank You

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# An Innovation Surcharge to Fund the Repurposing of Generic Drugs





# An Innovation Surcharge to Fund the Repurposing of Generic Drugs

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### Who am I?

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### The Opportunity: Innovation through Repurposing The Problem: Incentives The Idea: Innovation Surcharge Uses of Revenues from the Innovation Surcharge Making Progress on Policy Goals

# The Opportunity: Repurposing



Drug repurposing is an effective and cost-effective form of innovation

- The drugs already have RCT evidence of safety/efficacy in at least one indication. Hence the probability of successful application to other indications is higher than for new molecule
- The % of drugs that reach final FDA approval and market launch:
  - Success in Phase 2: 10% for all drugs, 25% for repurposed drugs
  - Success in Phase 3: 50% for all drugs, 65% for repurposed drugs
- Physicians can prescribe off-label for indications without authorized treatments, but this is done based on incomplete and circumstantial evidence. Repurposing and indication expansion studies extend the domain of evidence-based medicine.



#### Why do we see so few repurposing and indication-extension studies? There is inadequate funding from 'push' grants and 'pull' revenues.

- Push. The NIH and other entities can fund repurposing studies, using general tax revenues, but this competes with every other use of those funds. It also is at odds with the NIH culture of funding novel and potentially breakthrough research. Indication expansions are not sexy.
   Pull. Industry funds R&D using profits, which are obtained from drugs
- able to charge prices above costs. High prices are obtained only from drugs protected from competition by patents and/or FDA exclusivity. Generics are subject to fierce competition and generate no surplus for funding R&D, including repurposing

# The current R&D model is unsustainable

- Within the US, 92% of prescriptions are generic. Industry has raised prices on the remaining brands to an extent that payers are responding with aggressive measures.
- Insurers have responded to high prices on the remaining branded drugs by imposing administrative obstacles to physician prescription (formulary exclusions, prior authorization, step therapy)
- Employers have responded by imposing onerous consumer cost sharing (annual deductibles and percent coinsurance)
- These barriers to access are creating a crisis in physician frustration, failures of patient adherence and engagement, adverse health outcomes, and high transactions costs (\$100B/year minimum in US)
- The access restrictions are allowing PBMs to extract major rebates (40-50% off list price), reducing manufacturer funds for R&D

### Administrative Rules Impede the Ability of Physicians to Prescribe Expensive Drugs

#### Figure 3. Number of Unique Medicines Excluded From 1 or More PBM Formularies in Select Therapeutic Areas, by Year



Change in PA burden over last five years

**Q:** How has the burden associated with PA changed over the last five years for the physicians and staff in your practice?



Xcenda AmerisourceBergen. Skyrocketing Growth in PBM Formulary Exclusions. 2020.

### Patient Cost Sharing Drives Failures of Adherence and Adverse Health Outcomes

- Private insurers are shifting to percentage coinsurance, linked to the list (not net) drug price
- Medicare Part D plans impose coinsurance up to 33% and Part B requires 20%
- High cost-sharing requirements induce patients to abandon their prescriptions and suffer adverse effects

Figure 3. As Co-Payments Rise, Compliance with Drug Therapy Falls



SOURCE: Goldman et al., 2006. Used with permission. \*Average co-payment for each plan year is for a 30-day supply of cholesterollowering therapy.

### These Payer Strategies are Very Effective: Net Drug Prices Are Being Squeezed

Exhibit 24: Wholesaler Acquisition Cost (WAC) growth and net price growth for protected brands



Source: IQVIA Institute, National Sales Perspectives, Dec 2021; Bureau of Labor Statistics, Annual Average Monthly CPI Growth, Dec 2021.

# The Idea: Innovation Surcharge



- Drug repurposing studies need a funding source aside from general tax revenues and from profits derived from branded specialty drugs
- The obvious candidate: an innovation surcharge on generic drugs
- Even a \$1/prescription surcharge would generate \$6B/year. Compare this to the ARPA-H budget (\$2.5B) and NIH budget (\$45B)
- The surcharge could be collected from wholesalers/distributors.
- It would not affect consumer copays, since for generics these are small (average \$6.60) and not linked to price of drug (cost sharing for branded specialty drugs is very high)
- This would be a long term, predictable source of funding that could sustain repurposing studies that are initiated with seed funding from other sources

# **Use of Surcharge Revenues**

- Revenues from this surcharge would not accrue to the generic drug manufacturer but, rather, to a public entity such as NIH or ARPA-H. This entity would set up a mechanism to review proposals for indication expansion studies from startups, large firms, universities, laboratories.
- This dedicated surcharge is analogous to the fees that drug firms pay to FDA for market authorization (PDUFA, GDUFA). It is important to protect the funding from diversion to other uses of tax revenues
- The public entity need not limit indication-expansion grants to generics and biosimilars, but could extend them to branded products where there is little incentive for manufacturer-funded studies (e.g., brands approaching LOE)

# Conclusion



An innovation surcharge on generic drugs can accelerate progress towards multiple health and innovation policy goals

- Broaden the funding base to ensure the sustainability of R&D as generic market penetration continues to grow
- Direct investment towards drugs with the highest success in clinical trials
- Relieve the pressure on industry to raise prices on the shrinking number of branded drugs
- Relieve the pressure on payers to impose administrative (prior authorization) and financial (cost sharing) barriers to access
- Bring evidence-based medicine to patients currently treated off label

# **Further Reading**

#### VIEWPOINT

#### An Innovation Surcharge to Fund the Repurposing of Generic Drugs

James C. Robinson, PhD School of Public Health, University of California, Berkeley. The use of generic drugs continues to increase, generating substantial savings for purchasers and improving affordable access for patients. However, the expansion of generic drug use has come at the cost of a progressive narrowing of the financial basis for pharmaceutical innovation. Generic drugs do not contribute to research and development because competition drives their prices down to the costs of production and their profits down to the costs of capital. In contrast, brand-name drugs benefit from patent and regulatory protection from competition and pharmaceutical companies invest a portion of the resulting profits in new product development. Agency for Health (ARPA-H). Even a \$1 surcharge per dispensed generic prescription would generate almost \$6 billion per year, an appreciable supplement to the total NIH budget of \$45 billion and the initial budget of \$1 billion for the ARPA-H.<sup>1</sup> This revenue could easily be increased by small further raises to the surcharge.

The revenues from an innovation surcharge on generic drugs could be devoted to research and development for novel therapeutic compounds, but would have the greatest effect if devoted to the discovery of new uses for the generic drugs themselves. Pharmaceutical companies already invest in repurposing stud-

JAMA December 6, 2022 Volume 328, Number 21



### Using Interventional Pharmacoeconomics and Advance Market Commitments to Repurpose Generic Drugs with Cost

# Using Interventional Pharmacoeconomics and Advance Market Commitment to Repurpose Generic Drugs with Cost Savings

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### The Problem: Pharma will Not Fund Generic Drug Repurposing Clinical Trials due to Missing Incentives under the Patent System

- Not always commercially viable or possible to enforce a monopoly over a composition of matter by reformulating generic drugs or creating new method of administration.
- Method of Use patents cannot prevent physicians from prescribing off-label and pharmacies from automatically substituting a low-cost generic based on the active ingredient.
- **Patented formulations may be less effective** than the original formulation in a new indication but no business model to capture savings.
  - Generic racemic IV ketamine for treatment resistant depression with suicidal ideation (or rare indication) at \$2 a dose is arguably superior to patented esketamine for treatment resistant depression at \$850 a dose or \$50k+ p/a (Bahji, 2021).

#### The Solution: Interventional Pharmacoeconomics + Advance Market Commitments

- Interventional pharmacoeconomic design methodology funds RCTs via real-time cost savings by comparing equivalence or superiority of low-cost generic with expensive patented drug. If price difference is more than the cost-per-patient for sponsor, RCT has negative cost for a payer!
- Advance Market Commitments (AMCs) are a type of financially innovative <u>Pay-For-Success</u> (PFS) contract, similar to prizes conceptually, whereby a payer (insurers, government, etc.) only funds successful outcomes.
- Other types of PFS contracts include: Social Impact Bonds (SIBs) for public services, Subscription-Style-Payment (SSP) models for antibiotics, Pay-for-Performance for expensive cancer or orphan drugs, etc

>> Not yet implemented for repurposing generic drugs

>> Beacon proposed a generic drug repurposing SIB pilot to NHS in 2016 <u>https://www.rarebeacon.org/research/social-impact-bond/</u>

#### How the IVPE + AMC Model Works:

#### Step 1

 Payer signs Advance Market Commitment with Sponsor for funding RCT for repurposed generic drug. Possible to design interventional RCT comparing generic v expensive "best-in-class" intervention, where payer agrees to de-risk sponsor by transferring realtime cost savings.

#### Step 2

Sponsor raises private funds for RCT based on outcome payments agreed under AMC.
 Hybrid possible with support from public grants

#### Step 3

- Clinical Trial success
  - Sponsor receives AMC outcome payments + sales of "branded" generic
  - Payer saves healthcare costs (in excess of AMC outcome payments).
- Clinical Trial failure
  - AMC not triggered
  - Sponsor loses investment (unless risk offset from Payer sharing cost savings under IVPE RCT).

#### Example IVPE + AMC for Generic Drug Repurposing



### IVPE + AMC Model Overcomes Major Funding Hurdles Advantages vs. Traditional Direct Grant Funding

#### **Risk Transfer**

 Drug development is risky (<10% of success from Phase 1 RCTs). Impact investors are willing to take risks, less subject to bureaucratic restrictions. NB: IVPE de-risks impact investors / sponsors + payer!

#### **Better Technology**

 Pharma industry / CROs have access to market-leading tools and expertise to ensure efficient execution of R&D

#### **Free Market**

 Market forces incentivize investors to aggregate and efficiently allocate capital towards the clinical trials

#### **Scalable Cost Savings**

 Repurposed generics could outcompete patented drugs by providing lower cost per QALY for payers and overall better ROI for sponsors with cost savings shared between them to scale.

#### Other Problems with Public Funding of Generic Drug Repurposing

- Public grant funders need to "pick the winners" and take on all the risk of clinical trial failure.
   Risk of centralized "pork barrel politics"
- Private industry spends the most on clinical trials and has state-of-the-art technology and expertise to find generic drug repurposing "hits"
- Private industry clinical trials are typically larger and better quality than publicly funded clinical trials which are smaller and lower quality
- Darwinian pressure of the free market encourages "fast failure" and rewards only successful
  outcomes whereas grant funding has perverse incentives for grantee to not deliver and keep
  asking for additional funding

### Challenges with Interventional Pharmacoeconomics and Advance Market Commitments

- IVPE studies require low-cost intervention to substitute expensive standard of care. May be relatively small subset of IVPE use cases. Not all low-cost interventions medically indicated and may be difficult to get ethics approval to try alternative from expensive standard of care.
- IVPE might not address unmet medical need unless low-cost intervention may be an improvement over expensive standard of care. NB AMCs do not require expensive comparator, but require some calculation of future value of successful clinical trials (e.g. QALYs generated).
- AMCs require buy in from multiple key stakeholders learnings from LATAM and low-income countries.
- AMCs require funding secured in advance based on forecasted QALY value of future intervention. Time delay risk on payers due to requiring prediction of future QALYs / cost savings. Could require rebate if adverse events or recall in future or cost savings not realized due to change in standard of care.

## CONCLUSION

Interventional Pharmacoeconomics + Advance Market Commitments can create a financially de-risked business model for funding of clinical trials for repurposing of generic drugs to treat new (and rare) diseases by:

1. Transferring cost savings in real-time for payers to sponsors funding a IVPE RCT comparing the low-cost generic with patented drug where the price difference exceeds per patient cost of RCT;

2. Transferring risk of RCT failure to private impact investor;

3. If RCTs successful, sponsors receive under AMC that represents a small percentage of payers' future cost savings from updating clinical guidelines to reimburse low-cost generic in new indication, which allows business model to scale.

## **QUESTIONS?**

# <u>savva@crowdfundedcures.org</u> jcross@rymedi.com

https://twitter.com/CrowdFundedCure

Break









#### **CDRC Annual Meeting and Workshop Day 1: Tuesday April 18 Afternoon**

| Moderators: | Marco | Schito | and | David | Simon |
|-------------|-------|--------|-----|-------|-------|
|             |       |        |     |       |       |

- 1. Reimbursement by Public Payors– David Simon (Harvard)
- 2. Panel 2: RCTs, licensing, trial funding?
  - Patricia Van damme (Anticancer fund)
  - Amit Aggarwal (ABPI)
  - James Robinson (UCB)
  - Żaneta Zemła-Pacud (Polish Academy of Sciences)
  - Clare Thibodeaux (Cures within Reach)
  - Vikas Sukhatme (Morningside)
  - Cynthia Adinig (Patient)
- 3. Next steps (close of open session)

**Cochairs**: Rosie Lovett and Heather Stone

\*Closed session with with publicly funded programs

2:50 - 3:00 3:00 - 4:20

4:20-4:30

4:30 - 5:30

### **David Simon – Harvard**



### **Reimbursement by Public Payors**

# **Reimbursement by Public Payors**

David A. Simon, Harvard Law School (Northeastern University School of Law starting July 2023)





### The Reimbursement Landscape



### • Goals

- The Framework for Reimbursement
- Public and Private Insurance
- Medicare
- Takeaways





- Impress upon you that drug reimbursement is
  - Complex
  - Difficult
  - Designed (not always well!)
  - Expensive
  - Incentivization

### Framework for Reimbursement



- FDA Approval
- Insurance (Plan)
- Patient

Paying for Drugs – Insurance and Self-Pay



- Private Insurance
  - Employer sponsored plans
  - Private plans (through ACA marketplace)
  - Self-funded plans
- Public Insurance
  - Medicare
  - Medicaid/CHIP
  - Tricare (DoD)
  - Veteran's Affairs
- Cash
  - Cold hard cash
  - PBM-backed companies like GoodRx
## The Reimbursement Landscape



- Focus: Public insurance
  - Medicare
- Three Elements of Drug Insurance and Reimbursement
  - Coverage
  - Coding
  - Payment

## The Reimbursement Landscape



### • Medicare

- Part A Drugs During Inpatient Hospital Stay
- Part B Outpatient drugs administered by IV/physician injection
- Part C Medicare Advantage (Replaces A & B, and usually D)
- Part D Rx retail drugs

# Medicare Part A & B – Inpatient Hospitals & Outpatient



- Three methods of payment by CMS
  - Packaged payments
    - Most drugs
  - Pass-through payments (PTP)
    - New drugs
    - 2-3 year max
    - ASP + 6%
  - Separately payable drugs (SPD)
    - Not new drugs
    - More than \$130/day (2020)
    - Typically ASP + 4-6%
- Beneficiary responsible for 20% of payment
  - Usually coverd by medigap plan

## Medicare Part A & B – Inpatient Hospitals



- Part B spending over \$25 billion per year
- Pass through + separately payable drugs
  - Incentives to purchase more expensive drugs
  - Decreases amounts Medicare pays but not price
  - No incentive to use drugs with added clinical benefit
- Payment for Off-Label Cancer drugs
  - compendia
- Takeaway: \$5.1 billion in 2011 to \$12.9 billion in 2018 in PTP/SPD.
  - 82% of growth = cancer drugs

Medicare Part D (and C)



- Part D Retail Rx Drugs
  - Patient obtains at pharmacy
  - CMS sets general requirements of formularies
  - Prescription Drug Plans (PDPs) administer plans
    - Set formularies and reimbursement (tiers)
    - PBMs negotiate prices with manufacturers
      - compensated based on discounts to plans, incentive for manufacturer to raise prices
    - Implement cost control measures (PA, step therapy)
    - Paid by CMS lump sum for each beneficiary based on formula that accounts for health risks of patients
    - Catastrophic coverage CMS pays 80%, plan 20%; IRA changes this, plans cover more

# • If Part C plans offer Rx drug coverage, it must comply with Part D requirements

## Medicare Part D





NOTE: Total prescription drug spending accounts for rebates. SOURCE: KFF analysis of 2017 data from the National Health Expenditure Accounts.



## Part B & Part D Drug spending





A Relatively Small Number of Prescription Drugs Accounts for a Large Share of Medicare Part D and Part B Drug Spending







- Empowered CMS to negotiate prices for certain number of single-source drugs under Parts B & D
- Capped premium increases for Part D beneficiaries
- Require drug companies to pay rebates if prices outpace inflation
- Eliminated certain coverage gaps
- Increase Part D plan coverage requirements for catastrophic coverage

## Takeaways



- Reimbursement is complicated
- Reimbursement is big business (Parts B & D > \$180 billion)
- Reimbursement can affect
  - how firms price drugs
  - how PBMs negotiate drug prices
  - how plans decide to pay for drugs
  - how physicians and hospitals treat patients/use drugs
  - off-label use (e.g. oncology)
- As the IRA demonstrates, reimbursement (in Medicare) is a *choice*



David A. Simon, Harvard Law School (Northeastern University School of Law starting July 2023)

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#### Moderators: Marco Schito and David Simon

<u>Panel 2</u>:

- Patricia Van damme (Anticancer fund)
- Amit Aggarwal (ABPI)
- James Robinson (UCB)
- Żaneta Zemła-Pacud (Polish Academy of Sciences)
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#### CDRC Annual Meeting and Workshop Day 1: Next Steps Cochairs: Rosie Lovett and Heather Stone

\*Close of open session

- 1. Item 1
- 2. Item 2
- 3. Item 3

## **Closed Session**



### Beginning of closed session with with publicly funded programs





## **THANK YOU!**







## Final session: international collaboration







#### **FIRST KEY QUESTION**



#### **STRUCTURED INFORMATION SHARING**

NHS



#### **STRUCTURED INFORMATION SHARING**



#### **STRUCTURED INFORMATION SHARING: POSSIBLE CONTENT**



- Priority conditions and why they have been selected
- Horizon scanning/candidate identification: which medicines have been considered, reasons for not progressing
- Medicines being actively supported:
  - Progress updates
  - Requests for collaboration on international trials (matchmaking role between researchers?)
  - Barriers and solutions
- Policy/legislative work





## **THANK YOU!**







#2023CDRCMeeting