Biomedical E&I (BMEI-2022): Introduction & Orientation

November 01, 2022

Dmitry Kulish

Skoltech

Culture of Skoltech

- Speak English
  - Use every opportunity to become fluent
- CAP: Courteous, Actionable (non-descriptive), Positive
  - "It is raining outside so I need 10 mins to find an umbrella and then I join you"
  - "If you are really depressed by the color of my tie, you may consider bringing to me another one and convince me of its merits"
  - Rephrase and practice
- Reply and copy emails
- Check Canvas
- Turn on your camera
  - ZOOM culture +
  - Use the opportunity to train it !

→ **If you have any question, immediately raise your hand at any time: there are no stupid or inappropriate questions**
  → **asking & sharing is unique learning opportunity: volunteer often**

→ **Any digital activity in most classes (unless explicitly stated otherwise) is an illegal addiction that:**
  → **destroys your and your classmates learning experience**
  → **harms your leadership and innovation potential**
  → **leads to stress and possibly failure**

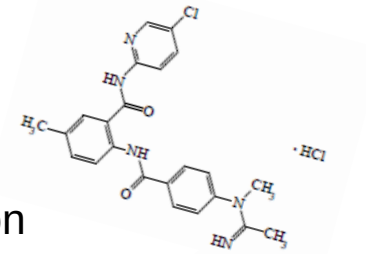
Canvas and E-mail are your lifelines

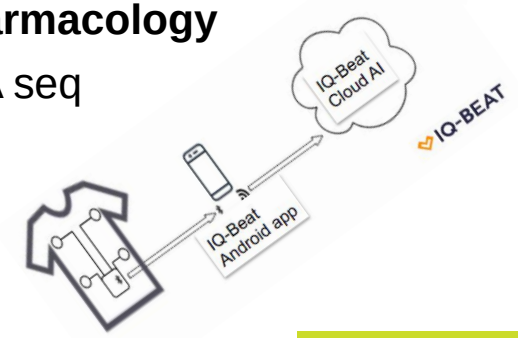
- Open it everyday at 7pm to receive crucial messages for the next day
  - Reply and copy stakeholders
- Follow Skoltech regs by proper emailing
  - e.g. clearances: DoE medical leave
- Four MUSTs of writing the letter:
  1. name yourself
  2. explain your issue
  3. suggest the possible solution
  4. suggest the form of feedback

> People who are funny and smart and return phone calls get much better press than people who are just funny and smart.
>
> Howard Simons

Dmitry Kulish, PhD, MBA

- **Skoltech Professor of the Practice, CEI**
  - “Innovation Workshop”
  - “Biomedical E&I”, “Nanochemistry E&I”
  - “Leadership & EQ hardcore games”
    - Best Prof – 2020 + 2021
- **IMG RAS / SUNY PhD Biochemistry**
  - JMB on GreB factor structure/function
- **Harvard postdoc Molecular Pharmacology**
  - MCB on RNA pol arrest DNA seq
- **Wharton MBA**
  - Business Strategy & Healthcare Mngmt
- **CEO of Pharmapark/Bioprocess**
  - the first Russian GMP-compliant biotech
- **Intel Capital Investment Director**
  - venture investment and management: Yandex, Evernote, GANht, Netflix





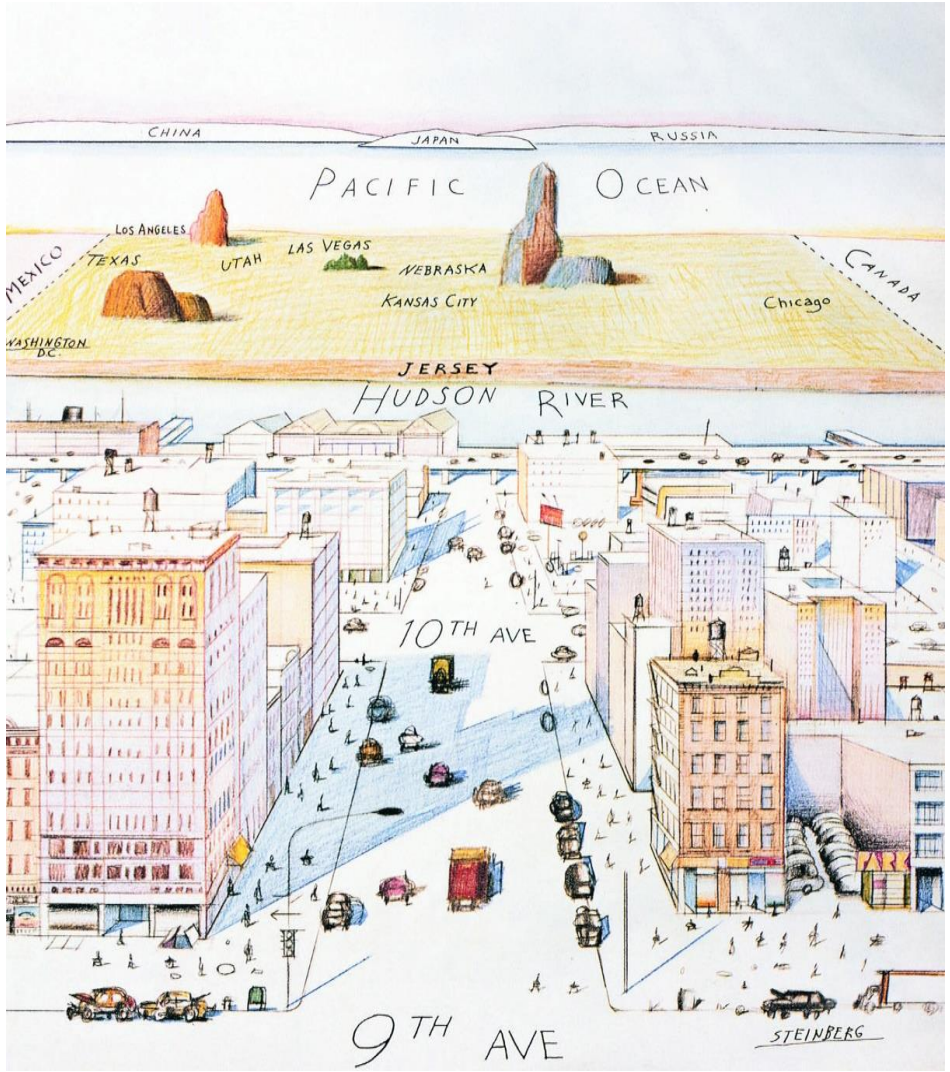
- **CEO and Founder of Neurok Pharma**
  - the second global VLP of HCV – killed by HIV FDA ban
- **B2B: R-Pharm – Nanolek – Binnopharm – DrugDevelopment.Ru**
  - Pharma Development: HCV, HIV, onco, antibiotics, and vaccines (incl COVID)
- **B2C: PLANDGE Publishing**
  - 2018: Two long lists of BOLSHAYA KNIGA
- **Angel Investing**
  - 6 (six) Skolkovo startups
    - **PHARMADIOL:** innovative anticoagulant
    - **SKINPORT:** painless microinjection array
    - **ONCODIAG**: carcinoma liquid biopsy with AI-MIS in cloud
    - **IQ-BEAT:** durable wearable cardiomonitor with AI-MIS in cloud
    - **RESOSTENT**: novel peripheral stent
    - **READERCHAIN:** cryptoreader with NFT marketplace with automatic ratings by AI-MIS in cloud

Sk Resident

www.DrKulish.com

Why you are at BMEI

- **LS students** (40%):
  - To see beyond the lab
- **non-LS students** (60%):
  - To learn the complex structure and spirit of biomedical value chain and innovation
  - Nobody in BM industry cares that you are non-LS or non-BM
- **MS-2 (55%):**
  - Return to another exciting project quest in an exciting team



BMEI COURSE CONTEXT

- Seeing the big picture (value chain) of biomedical industry
  - How your invention relates to the Biomedical innovation
  - Exactly who and why needs what you invented (PSC)

- Building the entire documentation set for the Biomedical innovation project
  - If you do not have the project, you may imagine (FAKE!) it

- Yes, it is kind of game
  - But playing it seriously takes significant effort and gives substantial learning that will help you both in science and in innovation

BMEI STRUCTURE AND TOPICS

- MONDAY
  - mentoring by request
- TUESDAY
  - lecture of the topic of the week
    - Indication + MOA + POC
    - Patent
    - Formulation + Manuf + QC
    - Reg guidances + Preclin + Clin
    - Value chain + Value delivery
- THUR
  - mentoring by request
- FRIDAY
  - Team presentation
    - **Last course activity day: Wed Dec 16th**

		TUE-FRI 9-12	
week 1	1	Onco/Tobacco game + BMEI course intro	
	4		
week 2	8	ELP	
	11	LECT: Indication + POC experiment + charact	
week 3	15	PRESO: Ind + POC experiment + valid QC	Michail Grubman
	18	LECT: Grubman	Michail Grubman
week 4	22	LECT: PATENT	
	25	PRESO: PATENT three claims	
week 5	29	LECT: Reg + Guidances + Preclin + Clin	
	2	PRESO: Reg + Guidances + Preclin + Clin	Sophia Yartseva
week 6	6	LECT: Formulation + Manuf + QC release	Sophia Yartseva
	9	PRESO: Formulation + Manuf + QC release	
week 7	13	LECT: BMEI career	
	16	FIN PRESOS	Michail Grubman

BMEI challenges

- **Unstructured learning beyond your area of expertise**
  - Intensive and tough
  - Advice will be provided, but the job is all yours

- **Project course setup**
  - You can not hide from constant work

- **Team dynamics**
  - Not always related to STE, very related to E&I

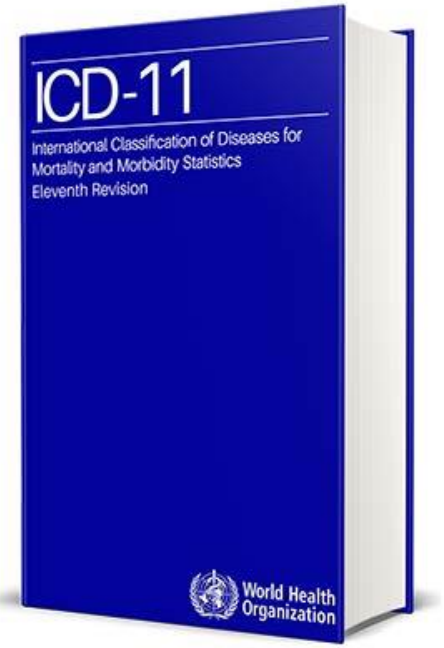
If you decide to stay at BMEI, you have to be ready to:

- **non-LS students will be flooded by the BioMed and Med terminology and concepts**
  - it is your job to keep up
- **LS students will be flooded by the IW-style teamwork under uncertainty**
  - that's E&I, you know
- **every Friday you present your project**
  - BMEI is quite intensive project-based course
- **most students report good experiences**
  - several striking examples (return, patents, non-LS)

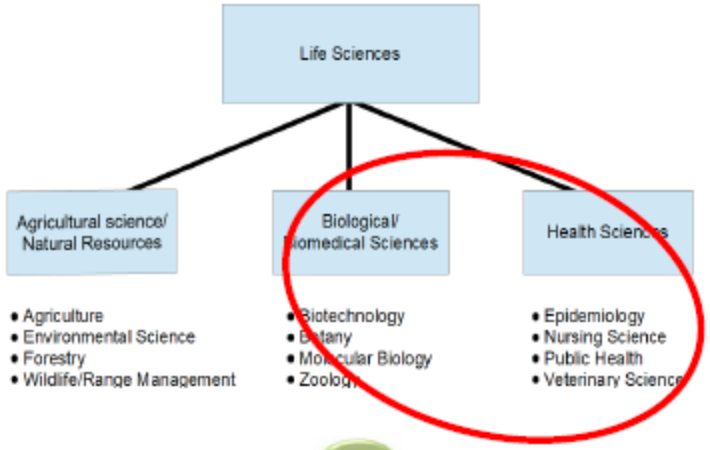
What is BioMedical E&I

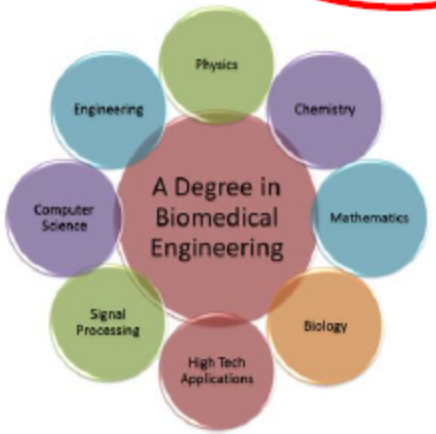
- **”Medical” means we treat a disease from ICD-11**
  - Therapy = drug or medical device
  - Prophylactics = drug or vaccine or med device
  - Diagnostics = medical device

- **“Bio” means our prototype is related to molecular biology**
  - Not agro, nor chemistry



DEFINE BIOMED PROJECT



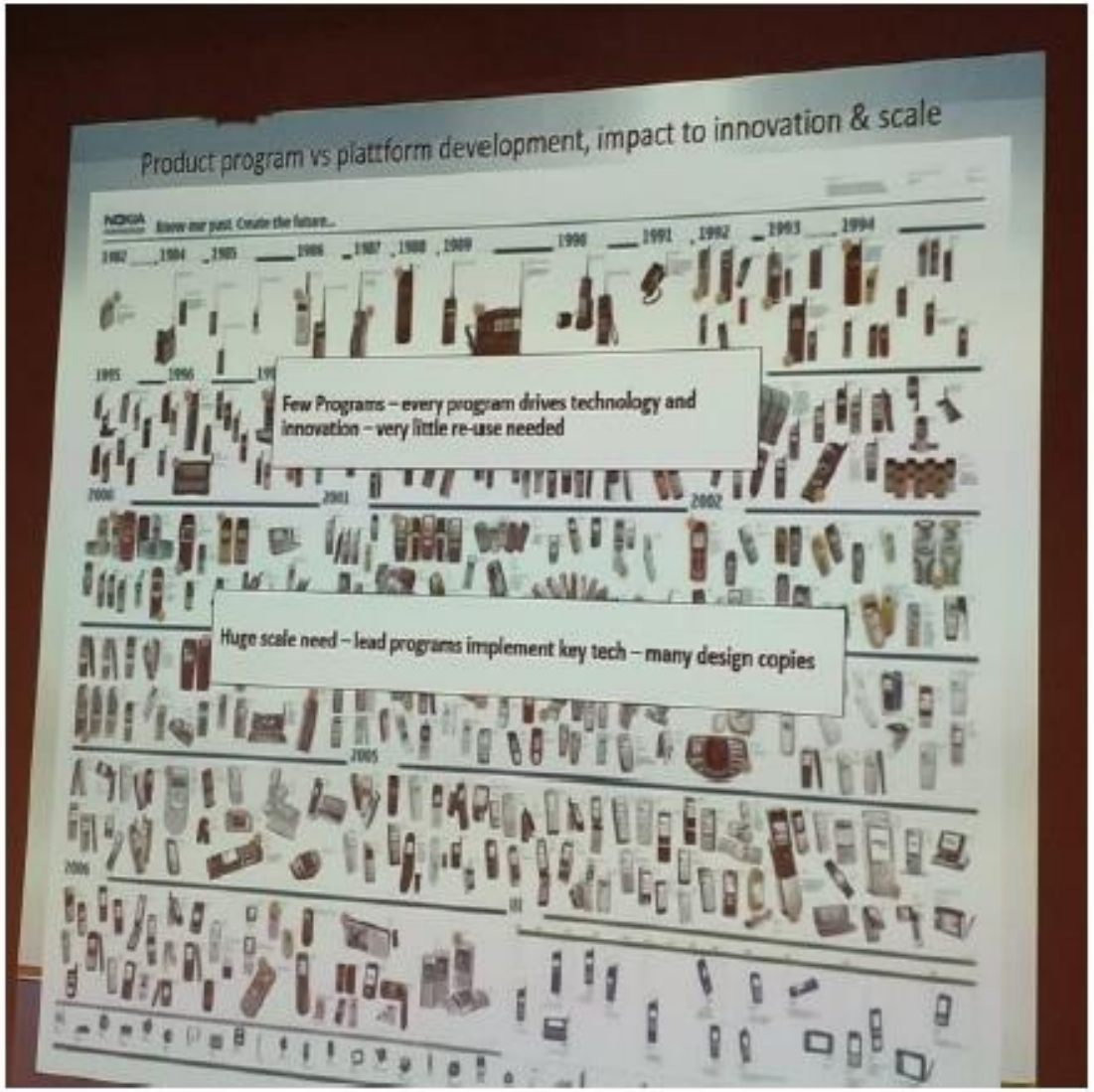


- Biomedical sciences are a set of sciences applying **portions of natural science or formal science**, or both, to knowledge, interventions, or technology that are **of use in healthcare or public health**.
  - **Key E&I segment of Life Sciences**
    - **for good or for bad**
  - Pharma + Diagnostics
  - Prophylactics + Biohacking
  - Devices + Services
- **Key differentiator: Disease to treat or prevent (a.k.a INDICATION)**
- Can non-Bio team do the BMEI project?
  - Sure! But the project components remain the same and require understanding of the disease and treatments

Why we separate BioMed E&I from all other E&Is

- **Most BioMedical products have end user benefits that are hard to see and quantify**
  - Only scientists and doctors can do that
  - Scientists and doctors become hybrid end users together with patients
- **Most BioMedical products have such a profound effect on society, that they must be strictly regulated**
  - Governmental regulators become another part of hybrid end user
- **Because of this hybrid nature of end user BioMedical product problem statement becomes so complicated that the mere fact of its definition guarantees commercial success**
  - **BioMed E&I risks are mostly product- and technology-related**
  - **All other E&I risks are mostly market-related**

Biomed EI vs the other EI - 1



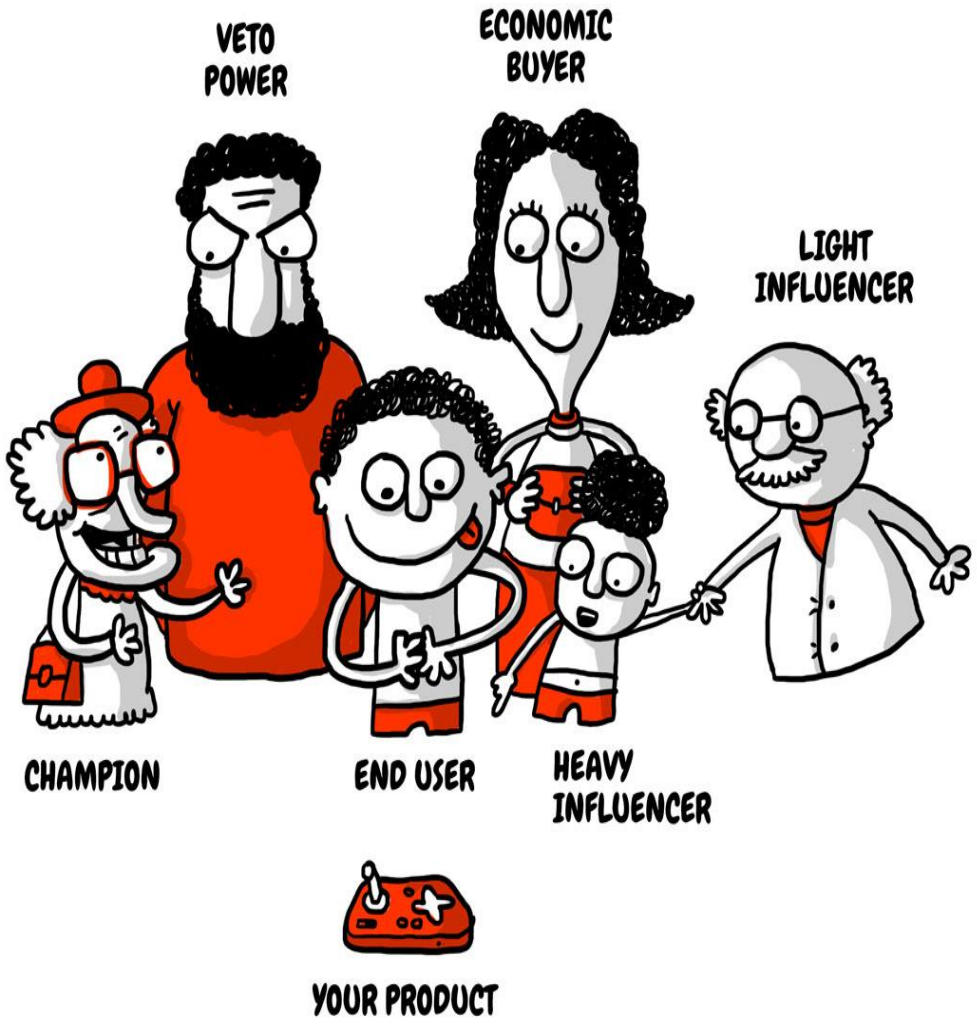
- BMEI B2C end user is ultra-complicated and conservative:
  - Patient
  - Doctor: trusted 3rd party
  - Governmental regulator
  - Pharmacologist (Drugstore)
    - You have to build very complicated product and validate it beyond any doubt
    - **GAMBLING is prohibited**
- BMEI B2B is beyond cost
  - If you bring your product to registration, if you satisfied all the stakeholders, somebody will buy it
  - **In BMEI we validate !**

Biomed EI vs the other EI - 2

TOPIC	GENERAL E&I	BIOMED E&I
PROBLEM STAKE HOLDER	Mostly one well-defined **END USER**	**Patient + Doctor + Regulator + Distributor**
BENEFICIARY VALUE	Mostly **FUNCTIONALITY**	**Functionality + MOA POC publications + Preclin/Clin reports + Manufacturing/QC documentation**
PRODUCT LAUNCH CYCLE	months	years
RISKS	Mostly **market demand**: If you produce something, there is no guarantee it will be purchased	Mostly **product launch**: If you managed to launch something in Biomed, someone will buy it, because if you reached the market, you are good enough

BUT ! STILL !

- **Registration of BioMed product or service is quite similar in nature to CustDev in “normal” E&I**
  - first you figure out the most acute problem you solve
  - then you build a prototype (called “preclinical experiment”) and discuss it with the market
  - **then you find doctors (KOLs) who agree to run your clinical trial**
  - **then you find regulators who agree to study your clinical data**
  - **then you register**
    - **after that you are almost guaranteed to have sales to these doctors and these regulators**



Class game to demonstrate all challenges of BMEI

- Quick learning of biomedical terminology and concepts
- Vicious Team dynamics
- Time pressure

Class Game Rules

- do not share your role descriptions with your peers and counteragents
- listen to your counteragents and remember that they got no obligations to you beyond common sense and general decency
- share your knowledge with you counteragents and engage in open discussions with them
- aim high to achieve your goals stated in your role description
- if you believe that the role description provides insufficient information, either raise hand and ask a question or reconstruct missing information based on your knowledge and common sense
- if you do not agree with your role thinking and position, feel free to adjust, but keep as close as possible to the basic assignment for the sake of the game

Part 1: PD1 inhibitors as treatment for lung cancer (NSCLC)

% treatment success	Cyto WHO standard	MSD PD1-MAB + (plus) PD1 test	BMS PD1-MAB - (without) PD1 test	FIERCE PHARMA
Lung cancer 1st line: naive (untreated) patients	15%			???
Lung cancer 2nd line: Cyto non responders	0	60%	60%	

Part 2: Heated tobacco smoking device

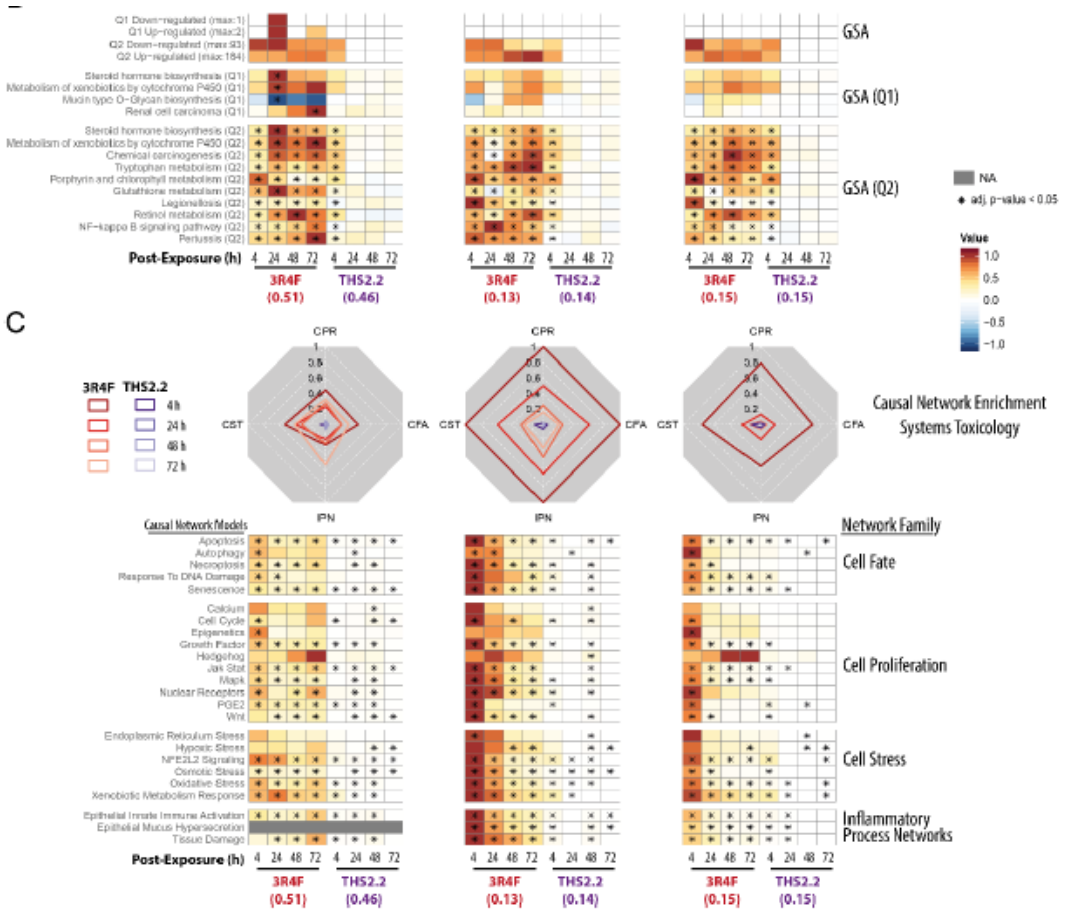


Figure 7. Mechanistic investigation of the exposure impact based on transcriptomics data.

(A) Barplots showing the number of significantly differentially expressed genes (DEGs) across the exposure conditions (FDR-adjusted p-value < 0.05). The heatmaps indicate the expression profiles of the top ten genes. The log2(fold-changes) compared with the respective air control groups are color-coded and the statistical significance level is indicated (FDR-adjusted p-value). (B) Gene set analysis (GSA) was performed with the KEGG gene-set collection using absolute log2(fold-changes) as the gene-level and the mean as the gene-set level statistics. Significance with respect to the treatment effect (Q2, compared with the air control) and dominant effects of individual gene sets (Q1) was assessed with Benjamini-Hochberg based FDR adjustment (FDR adj. p-value < 0.05). The numbers of significantly up- and down regulated gene sets for Q1 and Q2 are shown in the top panel, and the top gene sets are shown in the bottom panels. (C) The causal network enrichment approach for the analysis of the transcriptomics datasets. For each network category, the relative biological impact factor is shown in radar plots (CFA, Cell Fate; CPR, Cell Proliferation; CST, Cell Stress; IPN, Inflammatory Process Networks). The heatmaps show the network perturbation amplitudes for each network in the collection, across all conditions. Full details of the comparative analyses for all doses of the exposure are given in *Iskandar 2017c*.

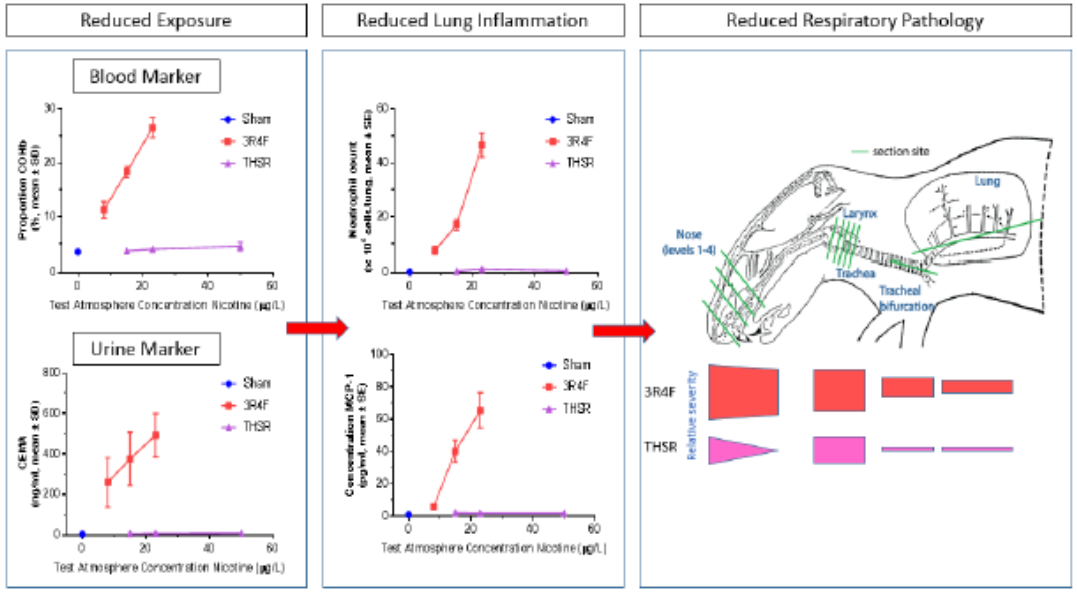


Figure 6: Summary of the 90-day inhalation study results. This *in vivo* study was conducted in rats to compare the toxicity of the THS aerosol with that of 3R4F smoke and a sham group (held in same conditions and exposed to filtered air). The reduced exposure to HPHCs leads to reduced lung inflammation, which in turn leads to reduced respiratory pathology findings. Abbr.: 3R4F = Reference Cigarette 3R4F, THSR = Tobacco Heating System, COHb = carboxyhemoglobin, CEMA = 2-cyanoethylmercaturic acid, MCP-1 = monocyte chemoattractant protein 1.

Sophisticated Break

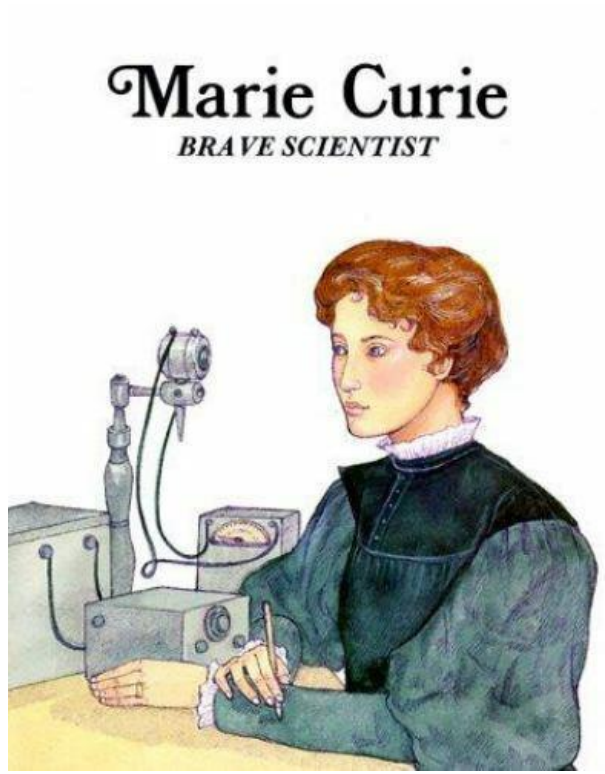
- **NOW: 10:30**
- **SCIENTISTS** stay
- **10:35 DOCTORS** come back in 5 minutes (from NOW)
- **10:40 REGULATORS** come back in 10 minutes (from NOW)
- **10:45 PATIENTS** come back in 15 minutes (from NOW)
- **then BREAK – YOU MUST READ YOUR ROLE**
- **EXERCISE starts in 30 minutes (from NOW)**

11:00

SCIENTISTS

SCIENTIST

		SMOKELESS TOBACCO PROHIBITION	
		NO	YES
ONCO DIAGNOSTICS APPROVAL	NO		
	YES	SCIENTIST	



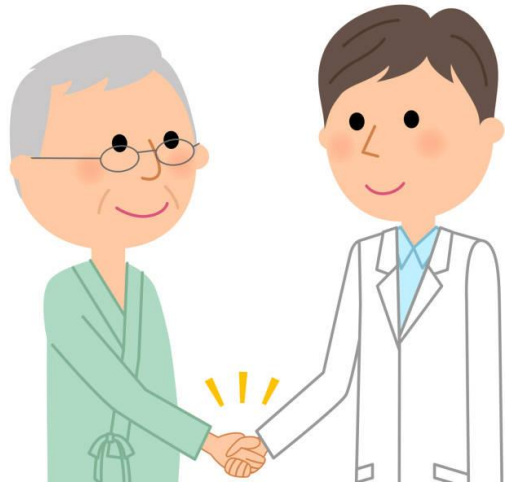
- **PD1 inhibitor case**
  - PD1 companion diagnostics is scientifically valid and mandatory. **Science must not be betrayed!**

- **Heated tobacco case**
  - It is well proven scientifically that heated tobacco inhalation in rodents is dramatically safer then the burning tobacco inhalation.

- **SCIENTIST ROLE DESCRIPTION:**
  - https://docs.google.com/document/d/1kl2lN3yEQ2NYc3Bx1UqHW61dmNth-G7YOfPlZrPz7LI

DOCTORS

DOCTOR



- **PD1 inhibitor case**
  - PD1 companion diagnostics is scientifically valid and makes sense

- **Heated tobacco case**
  - **Tobacco smoking is death.** It must be fully and totally prohibited. No discussion of ANY approval.

- **DOCTOR ROLE DESCRIPTION:**
  - https://docs.google.com/document/d/1gsULeyhK4t-cU2PZSfjNJY79RYwnJa3s04WLiOYMH34

		SMOKELESS TOBACCO PROHIBITION	
		NO	YES
ONCO DIAGNOSTICS APPROVAL	NO		
	YES		DOCTOR

REGULATORS

REGULATOR

- **PD1 inhibitor case**
  - PD1 companion diagnostics is scientifically unreliable and clinical data shows against it. Formally no need to approve.

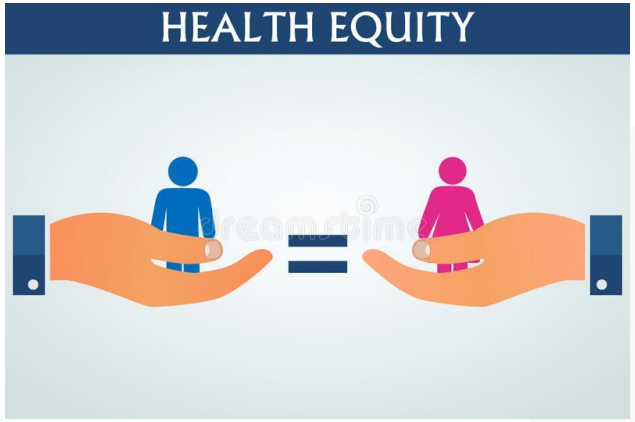
- **Heated tobacco case**
  - **Tobacco smoking is death.** Prohibition will hardly work, but it looks like the only option.

- **REGULATOR ROLE DESCRIPTION:**
  - https://docs.google.com/document/d/1o4R7isSzJgashESlxfz6_Jiwy4bdHNcZGeSR5gaSaRo

		SMOKELESS TOBACCO PROHIBITION	
		NO	YES
ONCO DIAGNOSTICS APPROVAL	NO		REGULATOR
	YES		

PATIENTS

PATIENT



- **PD1 inhibitor case**
  - PD1 companion diagnostics is scientifically unreliable and clinical data shows against it. **But most importantly it KILLS those people who are PD1-negative.** And it is needed to greedy pharmaceutical companies to make them money. PROHIBIT !!!

- **Heated tobacco case**
  - Prohibition of substance does not work and does not make sense. Do not thread on me! Let me decide how I kill myself !

- **PATIENT ROLE DESCRIPTION:**
  - https://docs.google.com/document/d/1jaLmdhtkbh_7mCYoJKuTt2o4rlanvTO3LrQTO5qN2r0

		SMOKELESS TOBACCO PROHIBITION	
		NO	YES
ONCO DIAGNOSTICS APPROVAL	NO	PATIENT	
	YES		

5 minutes:

Meet your peers.
Ask simple questions:

— How are you?

— What is your position on PD1-testing approval?
— What is your position on heated tobacco approval?
— What you want to achieve?

5 minutes:

DOCTOR TALKS TO PATIENT

REGULATOR TALKS TO SCIENTIST

5 minutes:

DOCTOR TALKS TO REGULATOR

PATIENT TALKS TO SCIENTIST

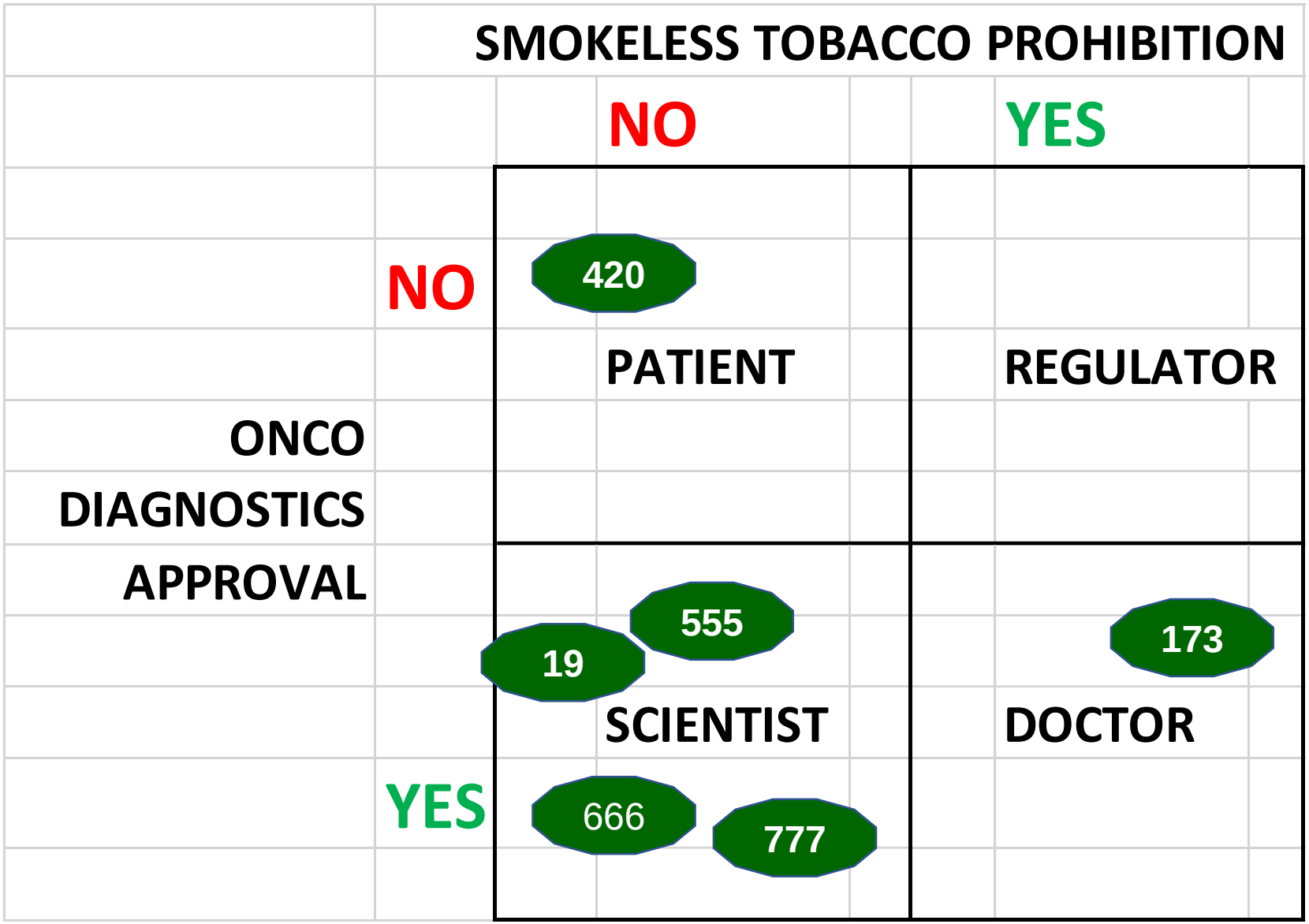
5 minutes:

DOCTOR TALKS TO SCIENTIST

PATIENT TALKS TO REGULATOR

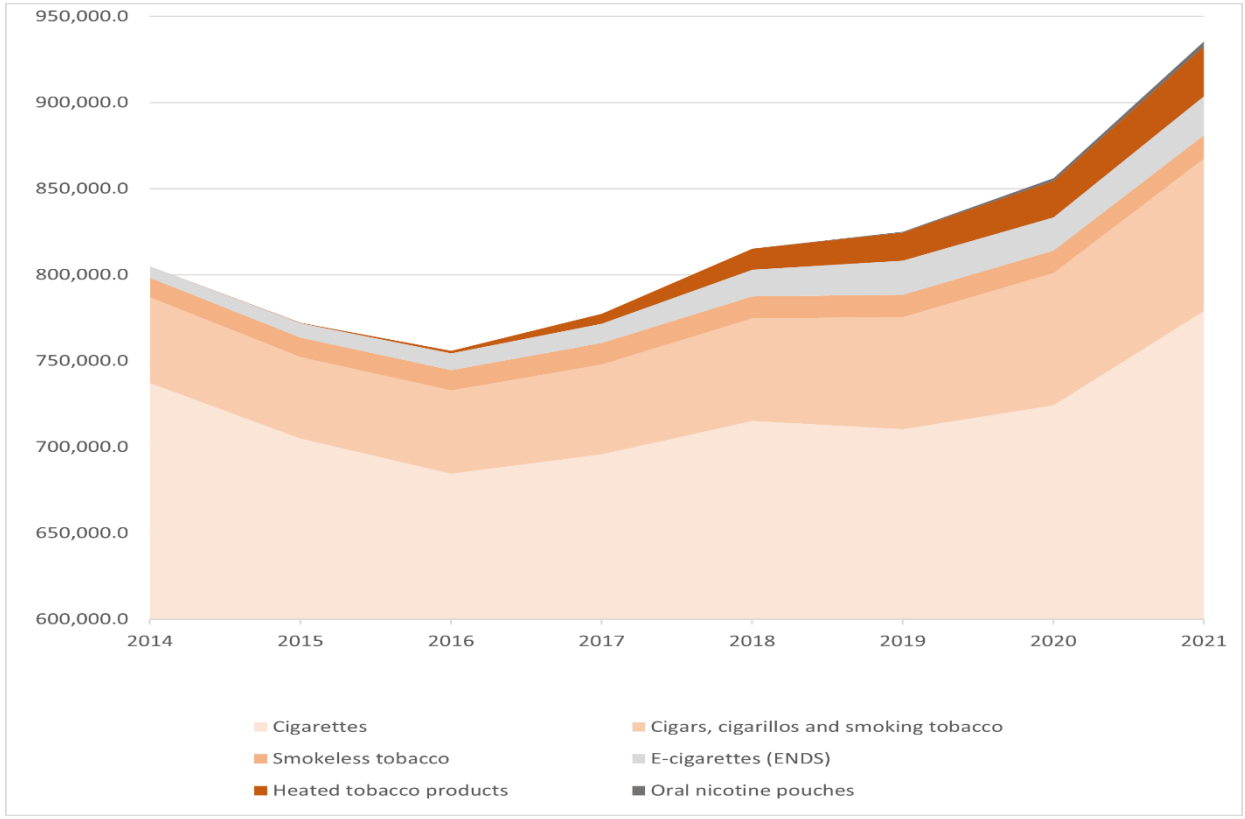
EACH PERSON FROM THE TEAM INPUTS THE TEAM CONSENSUS SOLUTION

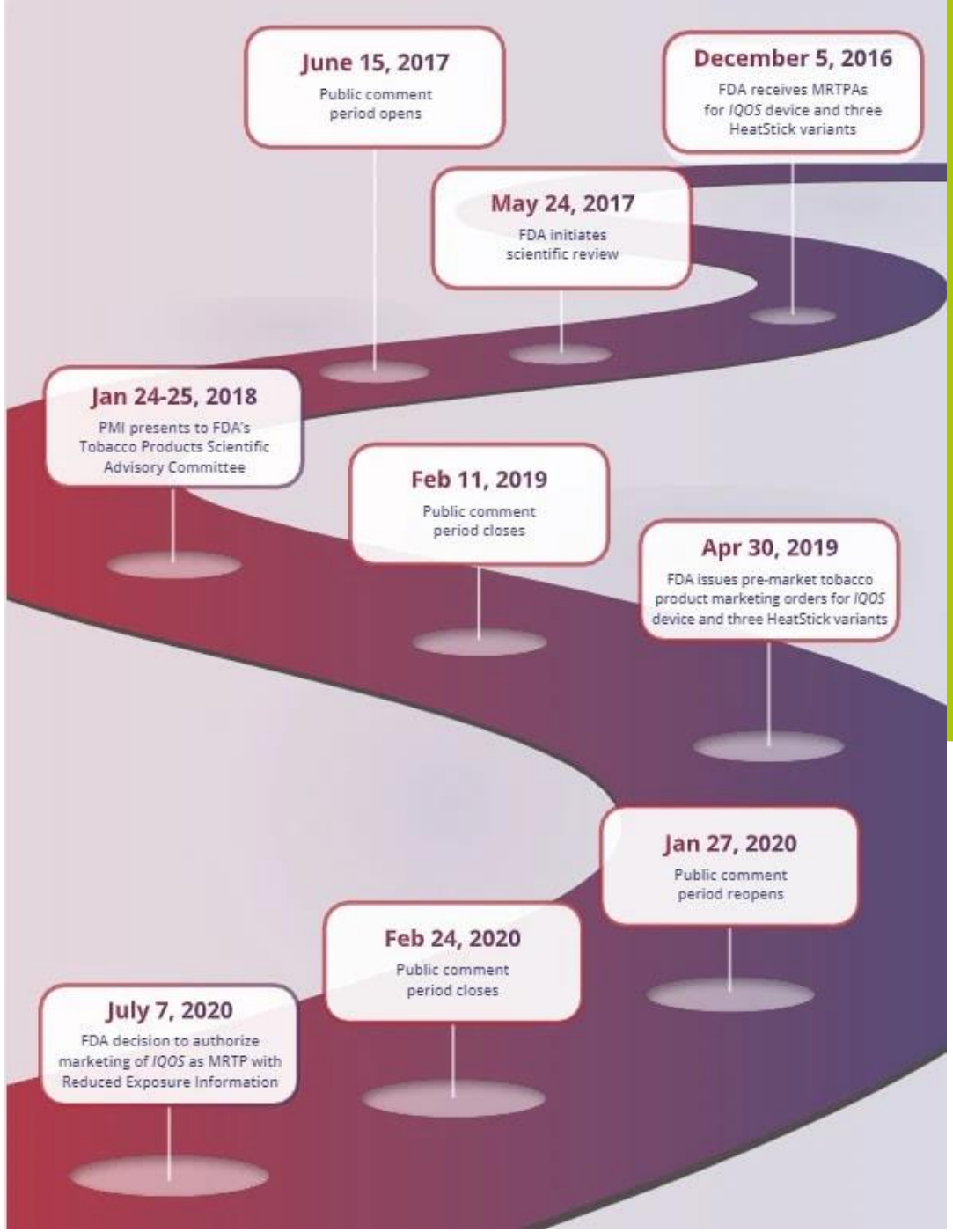
- **If even one person from the team fails to input, the solution is not found and YOU FAIL**
- https://forms.gle/PaFC3y85eWkEzgFFA


SMOKELESS TOBACCO PROHIBITION
NO
YES
NO
YES
ONCO DIAGNOSTICS APPROVAL
420
PATIENT
REGULATOR
555
19
173
SCIENTIST
DOCTOR
666
777

This was all real: onco

This was all real: heated tobacco





WHO IS SAVING LIFES HERE ?

	SMOKELESS TOBACCO PROHIBITION	
	NO	YES
NO	PATIENT	REGULATOR
ONCO DIAGNOSTICS APPROVAL		
YES	SCIENTIST	DOCTOR

WOULD YOU ARGUE ?

		SMOKELESS TOBACCO PROHIBITION	
		NO	YES
ONCO DIAGNOSTICS APPROVAL	NO		
	YES	SCIENTIST	

WOULD YOU ARGUE ?

		SMOKELESS TOBACCO PROHIBITION	
		NO	YES
ONCO DIAGNOSTICS APPROVAL	NO		
	YES		DOCTOR

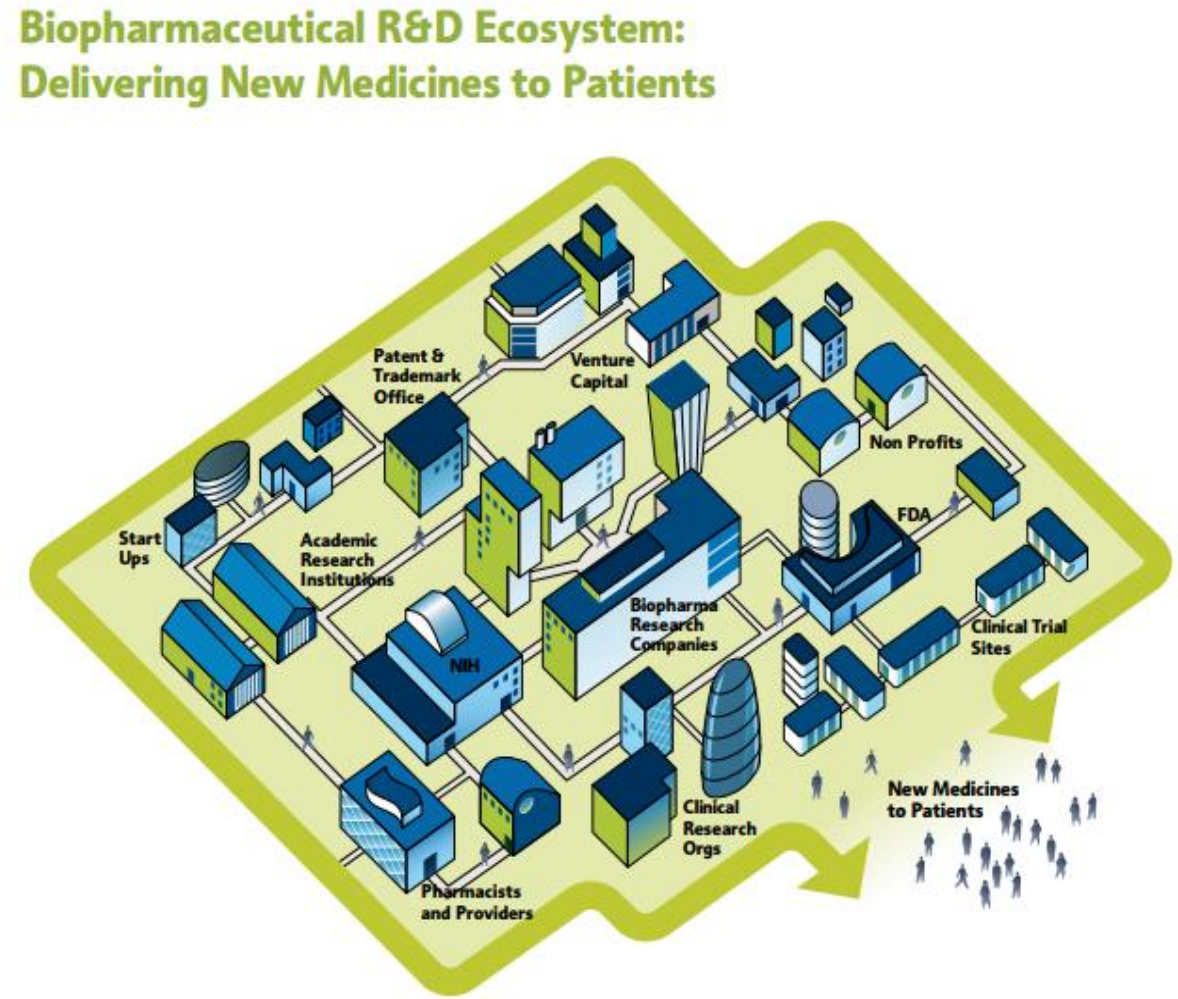
WOULD YOU ARGUE ?

		SMOKELESS TOBACCO PROHIBITION	
		NO	YES
ONCO DIAGNOSTICS APPROVAL	NO	PATIENT	
	YES		

WOULD YOU ARGUE ?

		SMOKELESS TOBACCO PROHIBITION	
		NO	YES
ONCO DIAGNOSTICS APPROVAL	NO		REGULATOR
	YES		

PD1 game learnings/sharings



- Who needs cancer cure?
- Who is beneficiary here?
- Who is innovator here?
- Who is decision maker here?
- What is the crucial component of PD1 innovation here?
- As Skoltech graduate, you wish to be in which position?

YOUR PITCH NEXT TUESDAY

- Google doc to fill personally (Mon evening deadline)
  - Non-confidential – mention only general things, not details
    - Your entry will be open for the class
    - 1 min pitch 2 min Q&A
  - **If you do not fill it, your BMEI grade goes down**

- Three questions
  - What is your expertise in BioMedical sciences? **(300 characters max)**
    Provide the title of your most recent diploma work.
  - Who beyond grant-eating scientists and profit-making doctors care about what you do in BioMedical sciences? Exactly which disease may be treated by what you do? **(500 characters max)**
  - What is your favorite BioMedical problem to solve? Who cares about this problem beyond grant-eating scientists and profit-making doctors? **(500 characters max)**
- Next Tue you must listen to all pitches from others !
  - **You will define your project and project team based on these speeches**

https://forms.gle/SGz1Sxq2L7ecVzRs7

thx.

Skoltech