Necessary Elements for Clinical Oral Mucositis Research of FDA-Regulated Products

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28 June 2018 Strauss 1-2

8:00 – 11:15

Mucositis Study Design Workshop: What do we need to know?

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Faculty Disclosure

X	No, nothing to disclose
	Yes, please specify:

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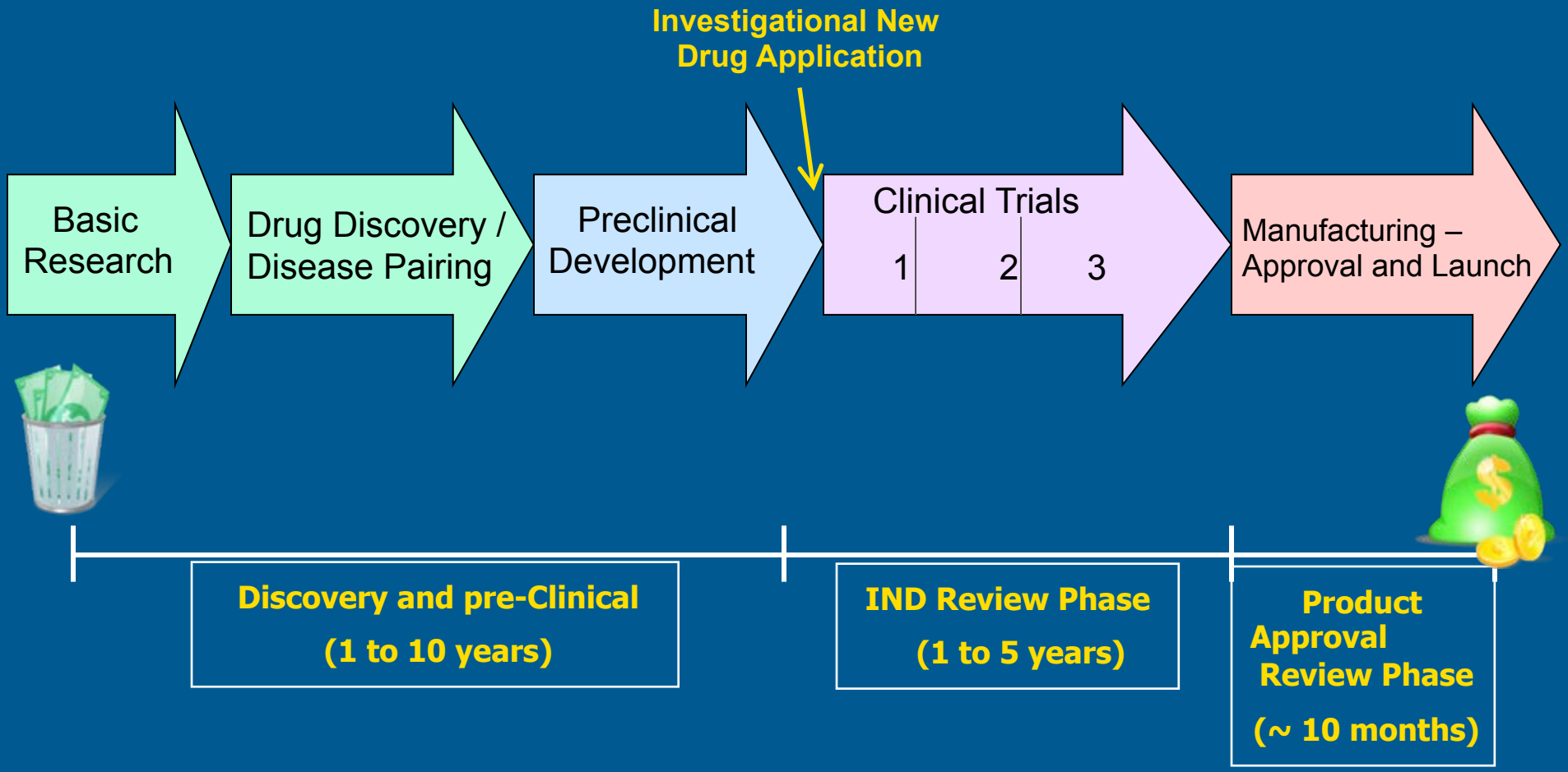
Clinical Research Pathway

(Drugs or Biologics)



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Device concept / prototype → Medical Device → Risk and Device Class Determination

510(k) Exempt

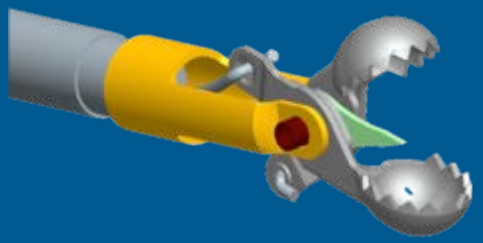
Is there a substantially equivalent predicate device on the market?

yes → 510(k) Premarket Notification

Clinical studies performed under IDE

Publications and other support

Premarket Approval



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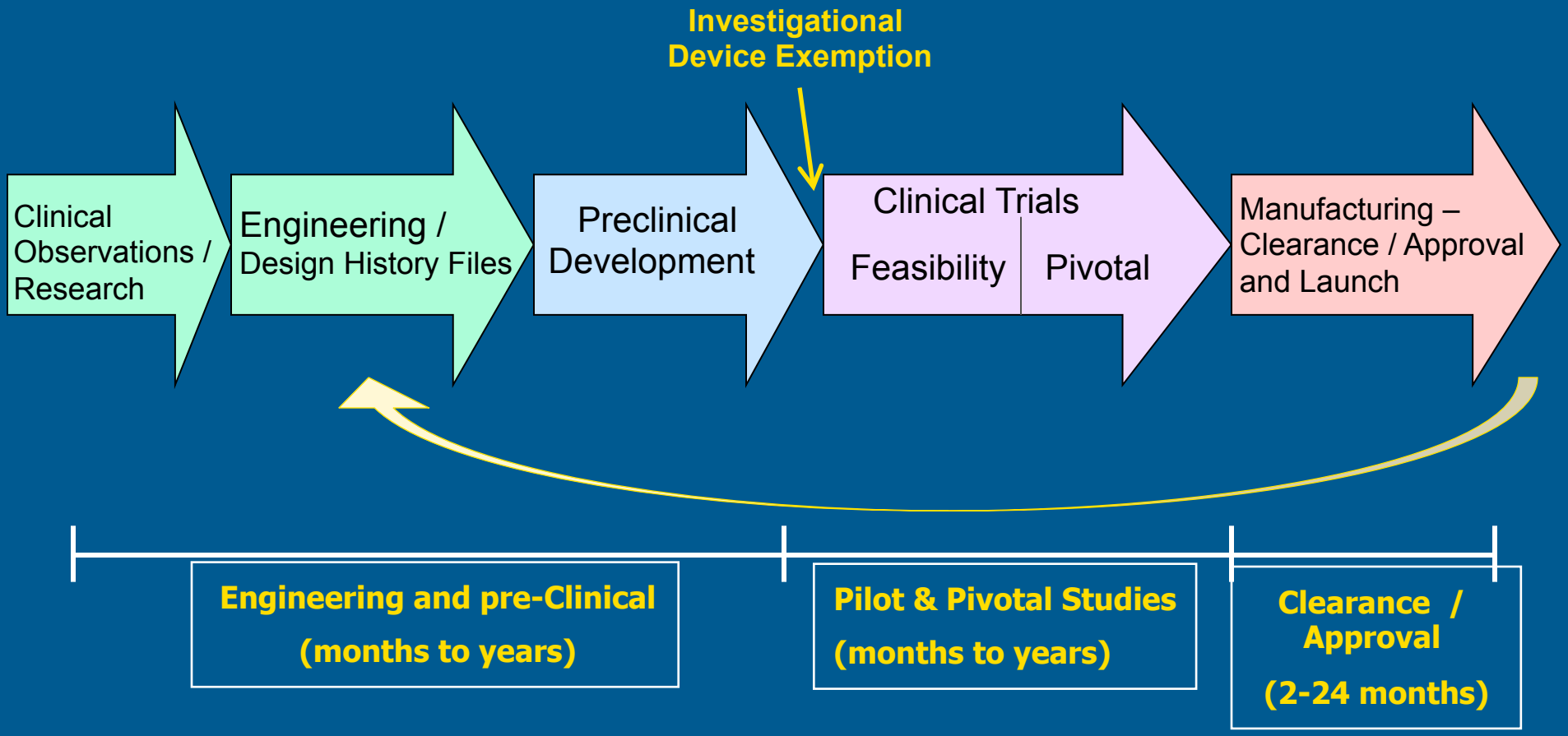
Clinical Research Pathway
(Devices)



Drug?

Device?

Biologic?

Isn't the type of product obvious?

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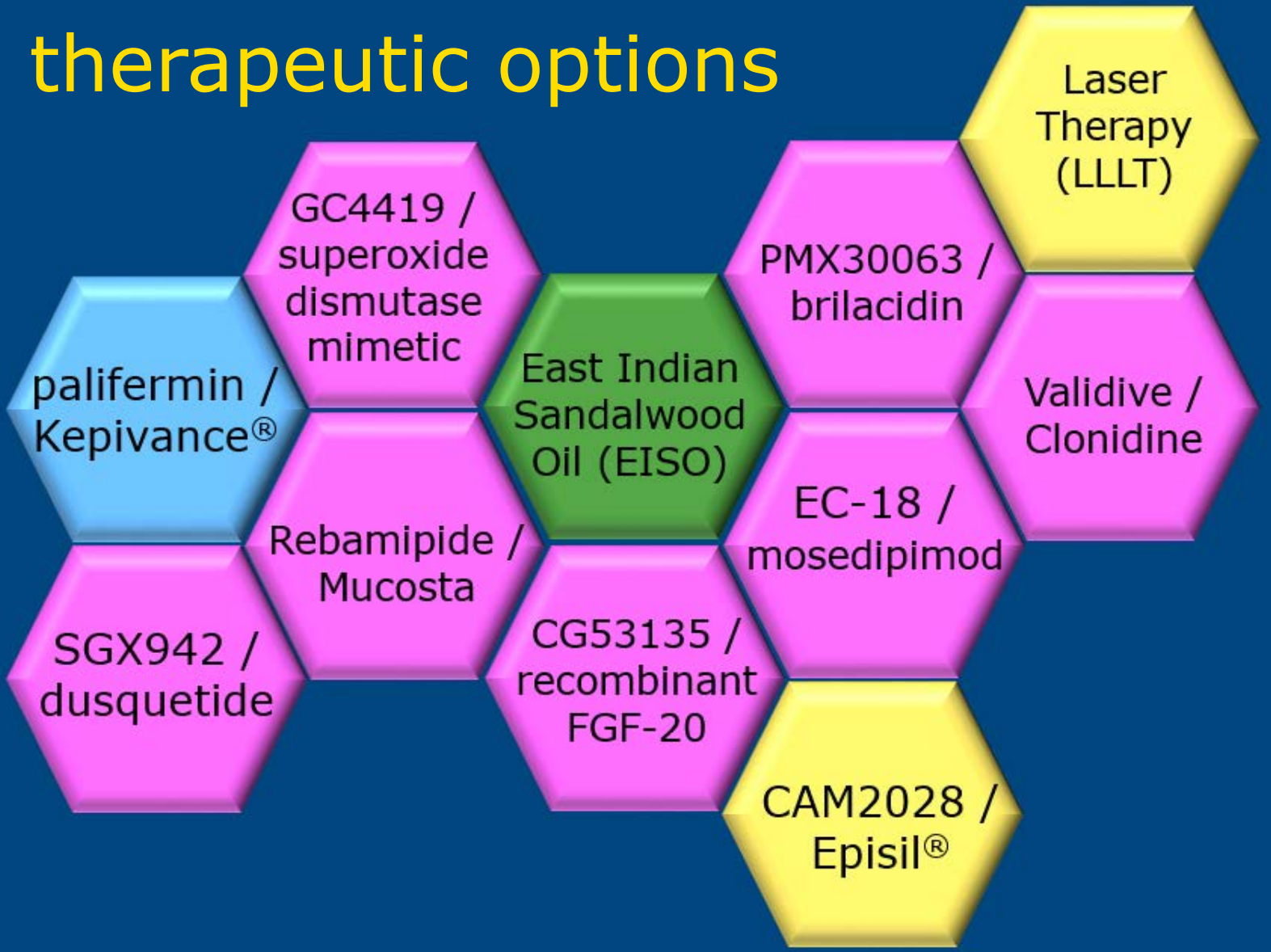
OM – therapeutic options



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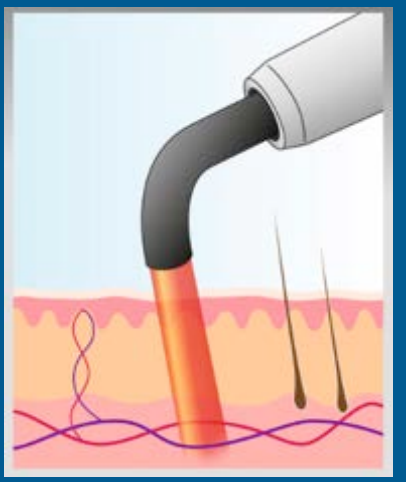
Photobiomodulation (PBM)

Low level laser therapy (LLLT) – may target a number of biological pathways:

- Proliferation
- Invasion
- Angiogenesis
- Metastasis



✓ may play a role in mitigating development of OM in chemoradiation patients.

episil®

- Contains glycerol dioleate and phosphatidylcholine (soy lecithin)

PMOA?
Primary Mode of Action

- Has no active pharmaceutical ingredient
- Classified as a wound dressing

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CAM2028 (episil®)

- Pre-clinical oral irritation studies in Syrian hamsters
- Clinical performance testing in bone marrow transplant patients suffering from OM

Cryotherapy + episil®	Cryotherapy alone

↓

- ✓ Had less pain
- ✓ Required significantly less pain medication
- ✓ Required less parenteral nutrition

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Case Study

episil®

Cleared through the 510k process (K101769)

Predicate device: Gelclair Concentrated Oral Gel (K013056)

Device Classification Name	Dressing, Wound, Drug
510(K) Number	K013056
FOIA Releasable 510(K)	K013056
Device Name	GELCLAIR CONCENTRATED ORAL GEL
Applicant	SINCLAIR PHARMACEUTICALS, LTD. 1 ALDER BROOK Chinley, High Peak, GB Sk23 6dn
Applicant Contact	Priscilla Cox
Correspondent	SINCLAIR PHARMACEUTICALS, LTD. 1 ALDER BROOK Chinley, High Peak, GB Sk23 6dn
Correspondent Contact	Priscilla Cox
Classification Product Code	FRO
Subsequent Product Code	MGQ
Date Received	09/11/2001
Decision Date	12/21/2001
Decision	Substantially Equivalent (SESE)
510k Review Panel	Dental
Summary	Summary
Type	Traditional
Reviewed By Third Party	No
Combination Product	No

Another common oral product that is a medical device . . .

Cavity varnish
21 CFR § 872.3260
Class 2 medical device

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Clinical Trial Process

1. Do you need to interact with the FDA?
2. When do you engage the FDA?
3. Do you need an IND (or IDE) to conduct your study?
4. What programs exist to expedite your drug development and review with the FDA?

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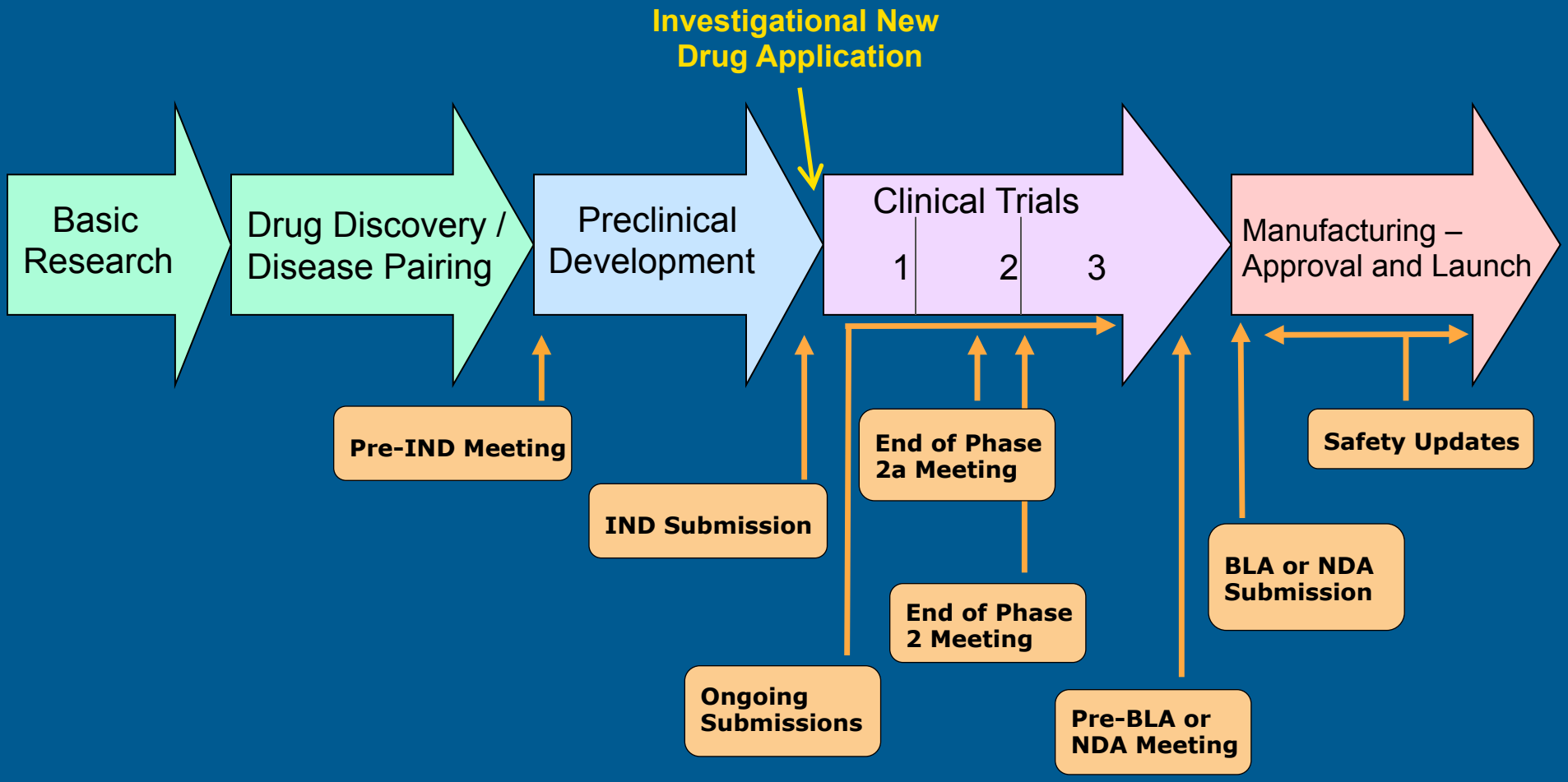
Clinical Research Pathway



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When to consider an IND exemption?

1. it is conducted in compliance with the requirements for IRB review

2. it is conducted in compliance with the requirements concerning the promotion and sale of drugs

3. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) of the drug product

4. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling or advertising for the drug

5. it does not intend to invoke exemption from informed consent

~ ALL of these criteria must be met ~

FDA's 30-day Process of Non-Objection for INDs

August 2018

Sun	Mon	Tue	Wed	Thu	Fri	Sat
29	30	31 Mail IND to FDA	1 FDA signs for it	2	3	4
5	6	7	8	9	10	11
		May not make it to the review division until some time this week				
12	13	14	15	16	17	18
		Potentially insurmountable issues might be communicated in advance . . .				
19	20	21	22	23	24	25
26	27 FDA internal meeting 	28 	29 	30 30-day review is up	31 Clinical Hold or Enroll	1

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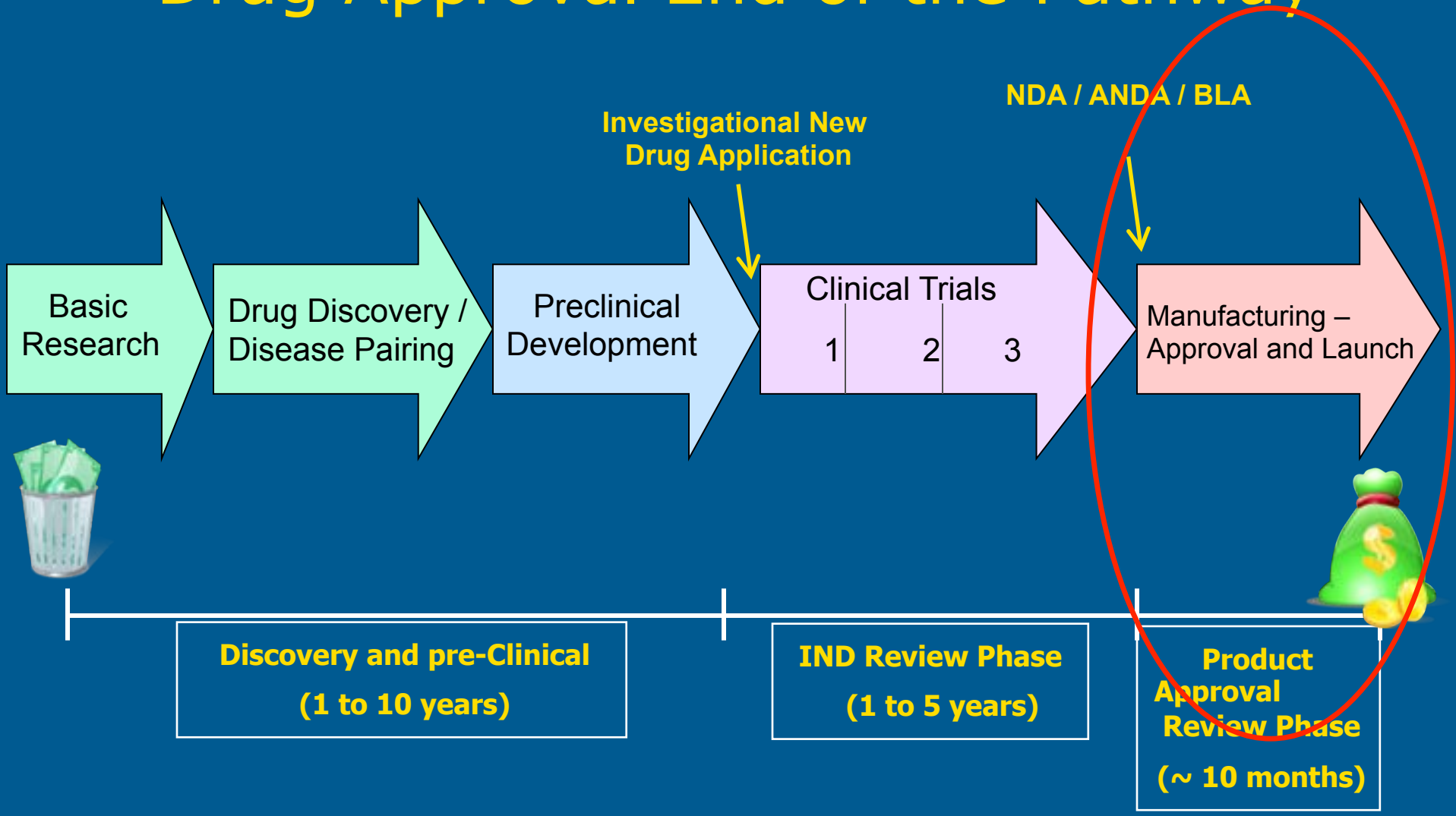
Drug Approval End of the Pathway



	Necessary Data	Data Must Demonstrate	Benefits to Sponsor
Fast Track Designation	• Preliminary nonclinical • Mechanistic or • Clinical data	Potential to address an unmet medical need for a serious condition	✓ More frequent meetings with FDA ✓ More frequent written communication from FDA ✓ Rolling review
Breakthrough Therapy Designation	• Preliminary clinical data	Substantial improvement on clinically significant endpoint(s) over available therapies	✓ Above three, PLUS ✓ Intensive guidance on an efficient drug development program ✓ Involvement of FDA senior managers to expedite development
Accelerated Approval Therapy	• Not specified; Sponsor should make justification of alternate endpoint based scientific support	Meaningful advantage over available therapies Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or earlier measured clinical endpoint	✓ Approval based on a surrogate or intermediate endpoint (often allows for shorter development time) ✓ FDA usually requires post-approval clinical trials to confirm clinical benefit
Priority Review Designation	• Data contained in the final NDA submission	Significant improvement in safety or efficacy of the treatment, prevention, or diagnosis of a serious condition	✓ Review of application in 6 months

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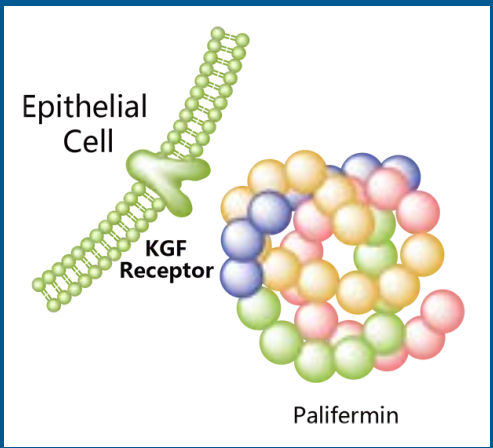
Case Study

Palifermin (Kepivance®)

- A biologic! Human keratinocyte growth factor
- Reduction of OM induced by myelotoxic, combined chemo- and radiotherapy
  - when given for hematopoietic stem cell transplantation
- Response is partially through epithelial proliferation and mucosal thickening
  - Cytoprotective and regenerative effects



December 2004

Palifermin (Kepivance®)

- Acute and subacute tox studies in rats and rhesus monkeys
- Multisite study – 212 patients with hematologic malignancies undergoing myeloablative chemotherapy and total body irradiation, with hematopoietic stem cell rescue

palifermin

placebo

↓

✓ Reduction in the incidence of severe OM
✓ Shorter median duration in those who had severe OM

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Palifermin (Kepivance®)

Fast Track status!

- ✓ Potential to address an unmet medical need for a serious condition

First-in-class biological product / BLA 125103

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GC4419 (Galera Therapeutics)

- Superoxide dismutase mimetic
- Converts superoxide to hydrogen peroxide and molecular oxygen
- Reduces deleterious effects of excess superoxide
- Phase 1 study: demonstrated safety
- Phase 2b study: locally advanced, non-metastatic squamous cell carcinoma of head and neck

Low dose GC4419

High dose GC4419

Placebo

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GC4419 for reduction of severe OM

Breakthrough Therapy Designation!

- ✓ Substantial improvement over currently available therapies, on clinically significant endpoints

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Supplements / Neutraceuticals

Research with a dietary supplement or botanical

- ✓ look at its effects on disease (to cure, treat, mitigate, prevent or diagnose a disease including associated symptoms)
- ✓ then you need to engage the FDA for an IND (or IND exemption) to govern the clinical study

The product is acting as a DRUG!

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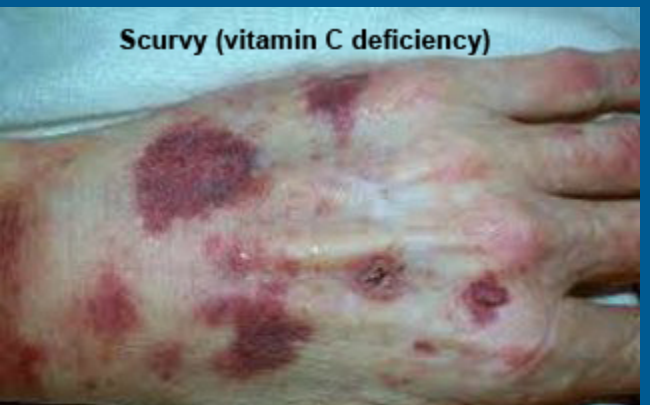
Supplements / Neutraceuticals

Evaluating the product as a dietary supplements

- ✓ structure / function claims
- ✓ then it is not a drug, an IND is not necessary

The product is acting as a Dietary Supplement!



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East Indian Sandalwood Oil

- Phase 2, open label study
- EISO used at 0.25% as a mouth rinse
- Prevention and treatment of OM induced by radiation therapy

Study enrolled seven subjects and closed in June 2017

https://clinicaltrials.gov/ct2/show/NCT02399228

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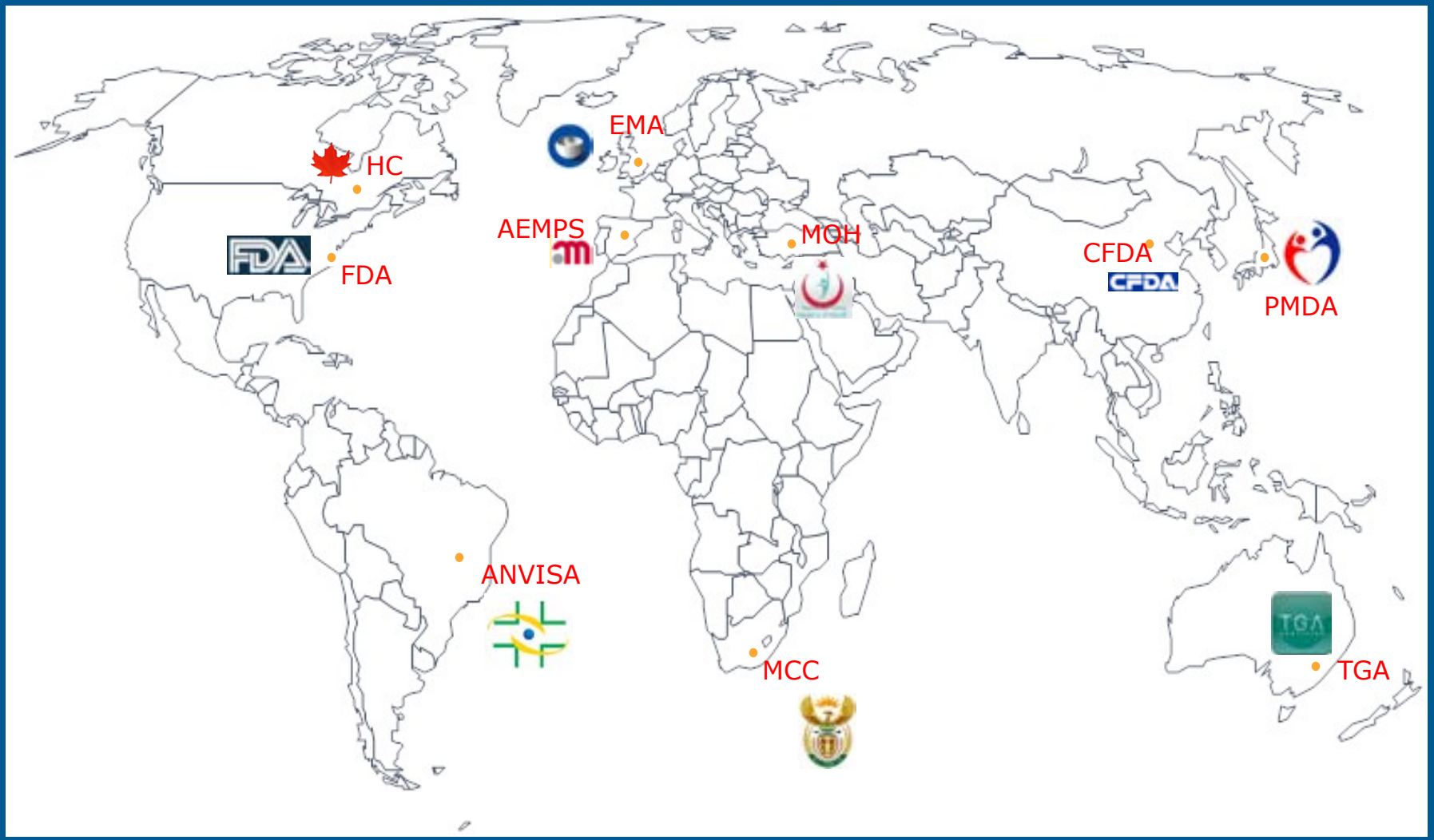
Around the world . . .



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SGX942 (Soligenix)

- Short synthetic peptide
- Innate defense regulator
- Modulates the body's reaction to injury and infection – pushing it to an anti-inflammatory and anti-infective response
- Accelerates resolution of tissue damage

Fast Track status!

SGX942 (Soligenix)

- Worked in tandem with the FDA and EMA for the design of their pivotal Phase 3 study
- Plans are for:
  - Double-blind, randomized, placebo controlled, multinational trial
  - 190 subjects with squamous cell carcinoma of the oral cavity

1.5mg/kg SGX942

Placebo

Take Home Messages

- Interact with the FDA early and often.
- If you have a creative study design, spend time with the FDA before and during the process.
- Know your product and understand the claims you want to make for it.
- Explore all the options for expediting the regulatory process to bring your important product to market.

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