

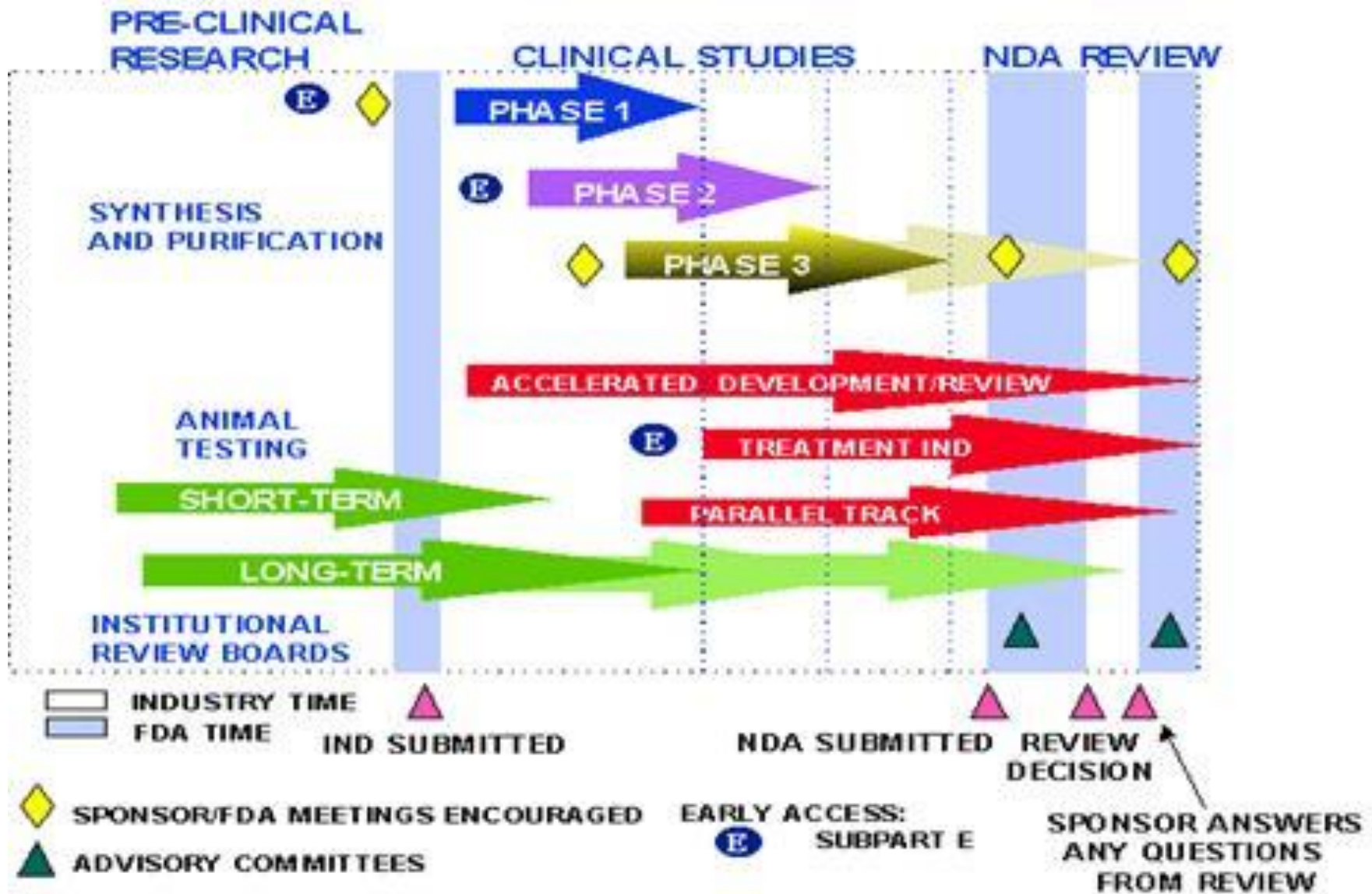
Regulatory requirements for "drugs" and chemicals -- the thinking behind the differences

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Outlines

- The difference between drugs and chemicals in registration or marketing
- Regulatory Toxicology
- regulatory programs for "drugs" and chemicals
- risk assessment guidelines
- regulatory influences on toxicology



US FDA Website

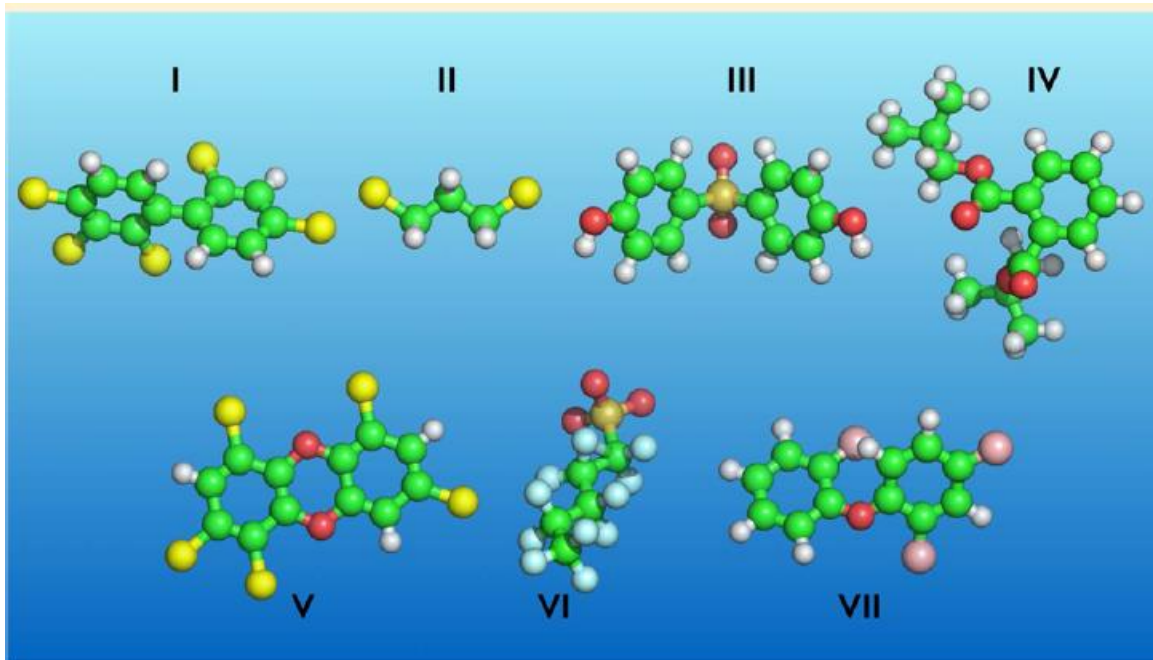
Lists non-clinical studies for “Drugs”

- Single-Dose Toxicity
- Repeat-Dose Toxicity (including supportive toxicokinetics evaluations)
- Genotoxicity
 - In vitro 1st toxicity dose to human dose
 - In vivo Costs 6.5 million (2011\$)
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Local Tolerance
- Other toxicity studies (antigenicity, irritation, immunotoxicity, dependences, etc.)

Chemical Properties, Environmental Fate, and Degradation of Seven
Classes of Pollutants

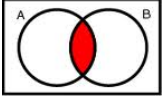
dx.doi.org/10.1021/tx500014w | *Chem. Res. Toxicol.* XXXX, XXX, XXX–XXX

- Polychlorinated biphenyls
- Halogenated hydrocarbons
- Estrogen analogues
- Phthalates
- Dioxins
- Perfluorinated compounds
- Brominated flame retardants



Some of these pollutants have been with us for more than 60 years. Why, the use of these pollutants were not evaluated before marketing?

Regulatory Toxicology

- Regulation  Toxicology
- How is toxicology applied in regulatory decision making.
- Regulatory agencies increasingly rely on toxicological science to **identify** potential hazards, **prioritize** potentially toxic substances, and provide **the data** used for **assessing risk**.

- Some programs, such as the US FDA for licensing **drugs, devices** and **food additives** and that of US EPA for registering **pesticides**, demand toxicology studies as a condition for marketing products.
- Regulatory programs have provided impetus for development and improvements in toxicology methods/assays.
- Government testing standards are influenced strongly by the prevailing consensus among toxicologists.

An Overview of Regulatory Approaches

- Premarket approval
 - FDA: drugs, medical devices
 - EPA: pesticides
- Premarket notification
 - EPA: new chemicals
- Require no premarket activity
 - FDA: cosmetics, foods
- Who has the burden of proof to demonstrate safety or hazard
 - Food additives: manufacture

Three different approaches to determine the level of exposure

- Acceptable Risk
- Balancing
- Feasibility/Best Available Technology

Acceptable Risk

- risk programs consider health evidence, therefore, toxicological data play a central role.
- For Non-carcinogens:
 - ADI (FDA), RfD (EPA) = NOAEL/SF
- Carcinogens can not be considered as “safe”, and no finite level of human exposure can be considered risk-free.
 - Safe thresholds may be established for some nongenotoxic carcinogens.

- Delaney clause (1958), food additive that has been shown to induce cancer in lab animals can not serve as a food additive.
 - a zero or negligible risk requirement
 - The 1996 amendment revoking the Delaney clause if the estimated cancer risk is extremely small (when it applies pesticide residue in foods)

Balancing Approaches

- Require the agency to balance the health benefits of risk reduction against the costs of such reductions. (Cost-benefit or risk-benefit analysis)
- TSCA (1976) is an example of a statute utilizing a balancing approach, requiring EPA set standards for toxic substances based on a quantified cost-benefit analysis.

Feasibility/Best Available Technology

- Require the agency to reduce exposures to the lowest feasible level, or to require companies to install the best available technology.

Regulatory Programs Utilizing Toxicological Data

US FDA

Foods

- FD&C Act (1958) Food Additives Amendments
 - The manufacture ...demonstrating ... “reasonably certain to be safe”...
 - Nonnaturally occurring food ingredients be exempted, GRAS (generally recognized as safe)

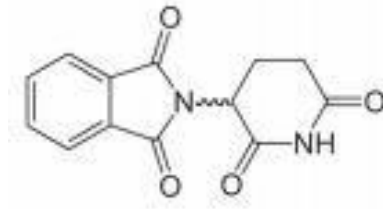
US FDA

Human Drugs

- The elixir incident (killed 107 people) led to the FD&C act of 1938
- the law authorized FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections.
- The Kefauver-Harris Amendments of 1962, which Revolutionized Drug Development

The change has to go
back to the Thalidomide
tragedy (1958)

The Thalidomide Tragedy



(沙利竇邁)

- To prevent morning sickness, used in the 1960s
- 1957 to 1962 in UK, Canada, Germany, Japan
 - US FDA did not approve
- 12,000 babies with phocomelia
 - if used in the 1st trimester
- 台灣有38名，大日本製藥於65、1、4日賠償。

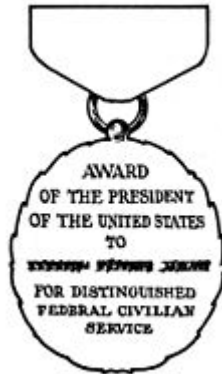




COVERSE



COVERSE



REVERSE
ACTUAL SIZE

- *Frances O. Kelsey, MD, the FDA medical officer who relied on the 1938 "new drug" law to refuse approval of thalidomide for marketing in the United States, receiving the **Distinguished Federal Civilian Service Award** from President John F. Kennedy, August 7, 1962.*



On October 10 President Kennedy signed the Drug Amendments of 1962, also known as the **Kefauver-Harris Amendments (Drug Efficacy Amendment)**, which was a response to the **Thalidomide tragedy in Europe.**

Thalidomide

IMPORTANT PATIENT INFORMATION



FDA (USA) relicenced this drug on Aug, 1998, to treat leprosy.

The major changes

- required the manufacturers to prove the **safety and effectiveness** of drug products before they go on the market (**premarket approval**), and afterwards to report any serious side effects.
- evidence of effectiveness based on adequate and well-controlled clinical studies conducted by qualified experts. Study subjects would be required to give their informed consent.

- mandated that FDA conduct a retrospective evaluation of the effectiveness of drugs approved for safety—but not for effectiveness—between 1938 and 1962.
- allowed FDA to set good manufacturing practices (GMP)
- transferred to FDA control of prescription drug advertising...
- controlled the marketing of generic drugs...

The Kefauver-Harris Amendments of 1962 leads to the birth of GLP

- The glory days
 - FDA prevented Thalidomide tragedy in US (1958)
- Scandals in CRO 1975 – 1978
 - Searle Laboratories case
 - Biometric Testing Incorporated
 - Industrial Bio-Test
 - performed 35-40% of all US toxicology studies!
 - 618/867 were invalid
 - falsified test procedures and data, and provided fraudulent reports of test results.

Another case: G.D. Searle & Company

- Produced several major pharmaceutical and food products: Flagyl (Metronidazole), Aldactone and aspartame
- A researcher submitted an article to Journal of National Cancer Institute (JNCI), which showed that Flagyl (metronidazole) caused cancer in his animal study
- Discrepancies between individual and summary data

- Inspection began on October 6, 1975 and continued until December 19, 1975
- Six teams of FDA investigators were assigned to investigation
- Investigation was estimated to have taken eleven person-years to complete

- Problems

- Lack of personnel training, deviations from study protocols, unexplained discrepancies and changes to data (SOP), lack of quality control (品管) of reported data, lack of quality assurance (品質、質量保證) procedures, among others.

- These lead to the GLP (優良實驗室操作規範)

Good Laboratory Practice (GLP)

- As results, FDA decided to regulate laboratory testing
 - Proposed (in Federal Register) on 11/19/1976
 - Final 12/22/1978
 - Effective 6/20/1979
 - FDA GLP major revision 9/4/1987 (21 CFR Part 58)
 - GLP revision 2014 or 2015 (**pending**)
- US EPA GLP issued 8/17/1989 under FIFRA (40 CFR Part 160) and TSCA (40 CFR Part 792)
- 凡走過必留下痕跡。

GLP

- GLP regulations are not a set of "How To" rules
- The regulations are a set of principles
- GLP regulations do not assure "Good Science"
- GLP are a **management system** to ensure the **quality and integrity** of the data underlying a study

US FDA

Medical Devices

- FDA has authority to regulate the testing, marketing, and use. (FD&C Act 1976)
- 3-tier control, and the premarket approval for a class III device is similar to that required for new drugs. The sponsor must demonstrate **safety** and **efficacy**.

US FDA

Cosmetics

- No premarket approval, though many manufactures routinely do so.
- The basic safety standard is “no product may be marketed if it contains “a poisonous or deleterious substance, which may render it injurious to health”.
- CIR (Cosmetic Ingredient Review), a private expert assessment body

US EPA

Pesticides

- Registration is under FIFRA (Federal Insecticides, Fungicides, and Rodenticides Act) 1972
- Tolerance is under FD&C Act, which sets the allowable level in foods.
- If the pesticide is a carcinogen, the Delaney clause prohibited its approval in the use. However, this was revised by Congress in 1996 by the Food Quality Program (FQPA) to exempt pesticide residue from the operation of the Delaney clause.

US EPA

Industrial Chemicals

- The TSCA of 1976 provides EPA with authority to require reporting, record-keeping and **testing requirements**, and restrictions relating to **chemical substances and/or mixtures**. Certain substances are generally excluded from TSCA, including, among others, food, drugs, cosmetics and pesticides.
- TSCA empowers EPA **to require testing** to develop the necessary data.

- TSCA requires anyone who plans to manufacture (including import) a new chemical substance ...to notify EPA with notice.... This premanufacture notice (PMN), must be submitted at least 90 days prior to the manufacture of the chemical.
- In contrast, the EU is implementing a much more aggressive regulatory program for chemical substance as the **R**egistration **E**valuation, **A**uthorization, and **R**estriction of **C**hemical Substances program (REACH).

REACH

(Registration, Evaluation, Authorisation and Restriction of Chemicals)

- 是指歐盟於2006年12日公布之規章，是針對化學品註冊、評估、授權及限制的一套整合體系。
- 要求化學物質製造商及進口商，於製造或進口前必須註冊登錄。
- 業者有義務申報使用該化學物質的風險以及所採取之適當管理措施。
- 逐漸取代危險化學物質。

Environmental Protection Agency
Administrator Russell E. Train today stated that the recently enacted Toxic Substances Control Act is "one of the most important pieces of 'preventive medicine' legislation" ever passed by Congress. He said this is because "its basic aim is to give public health far more of the weight that it deserves in the decisions by which chemicals are commercially made and marketed, by which they enter and spread throughout the human environment."

[EPA press release - October 21, 1976]

毒性化學物質管理法

民75、11、26日總統公布

- 立法院於民國102、11、22日三讀通過《毒性化學物質管理法》修正案，總統並已於同年12月11日公布。
- 這次修法建立我國**化學品登錄制度**，以及毒化物釋放量紀錄資訊公開。
- 訂出既有化學物質及新化學物質，規定既有化學物質及新化學物質於登錄後始得製造或輸入，新化學物質須經實質審查。

新化學物質需經實質審查才准予製造或輸入

- 我國以往對新化學物質沒有任何事先審查機制。相對美國TSCA有PMN，包括化學辨識、產量、副產物、使用、環境釋出、廢棄處置方法以及人類暴露等。
- 現在新化學物質進入市場之前，環保署規定其使用條件，甚至禁止其生產，減少對人類健康及環境之潛在風險。
- 在登錄後，必須經過初步評估審查判斷其危害並進行必要的限制或管制後，才能准予輸入或製造。但是方法則仍不明。

毒化物釋放量資訊必須上網公開 化學物質登錄資訊必須全面公開 新增奈米物質之登錄規定

- 我國目前共有7.9萬多種化學物質於市面上流竄，每年約增加100多種新化學物質。
- 面對龐大的化學品登錄資料，以目前主管機關的人力不足以肩負此責任。
- 這次修法只是在《毒管法》中增訂幾個條文確立主要原則，但仍缺細則。