Hormesis and the Pharmaceutical Industry Research and Development (Part Two)

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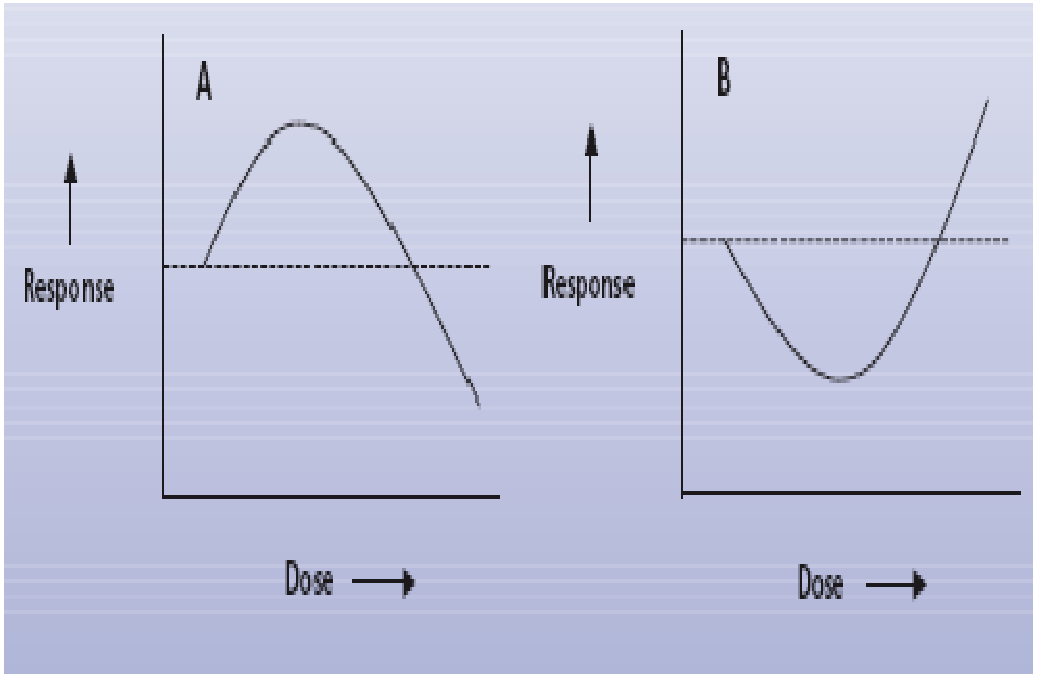
Because health matters

Presentation Overview

- Hormesis and the literature
- Implications and challenges for the pharmaceutical industry
- Common failures in drug development
- Some solutions by phase of drug development
- Regulatory guidelines for industry
  - Take Home Messages
- Concluding remarks

Hormesis – Traditional definition



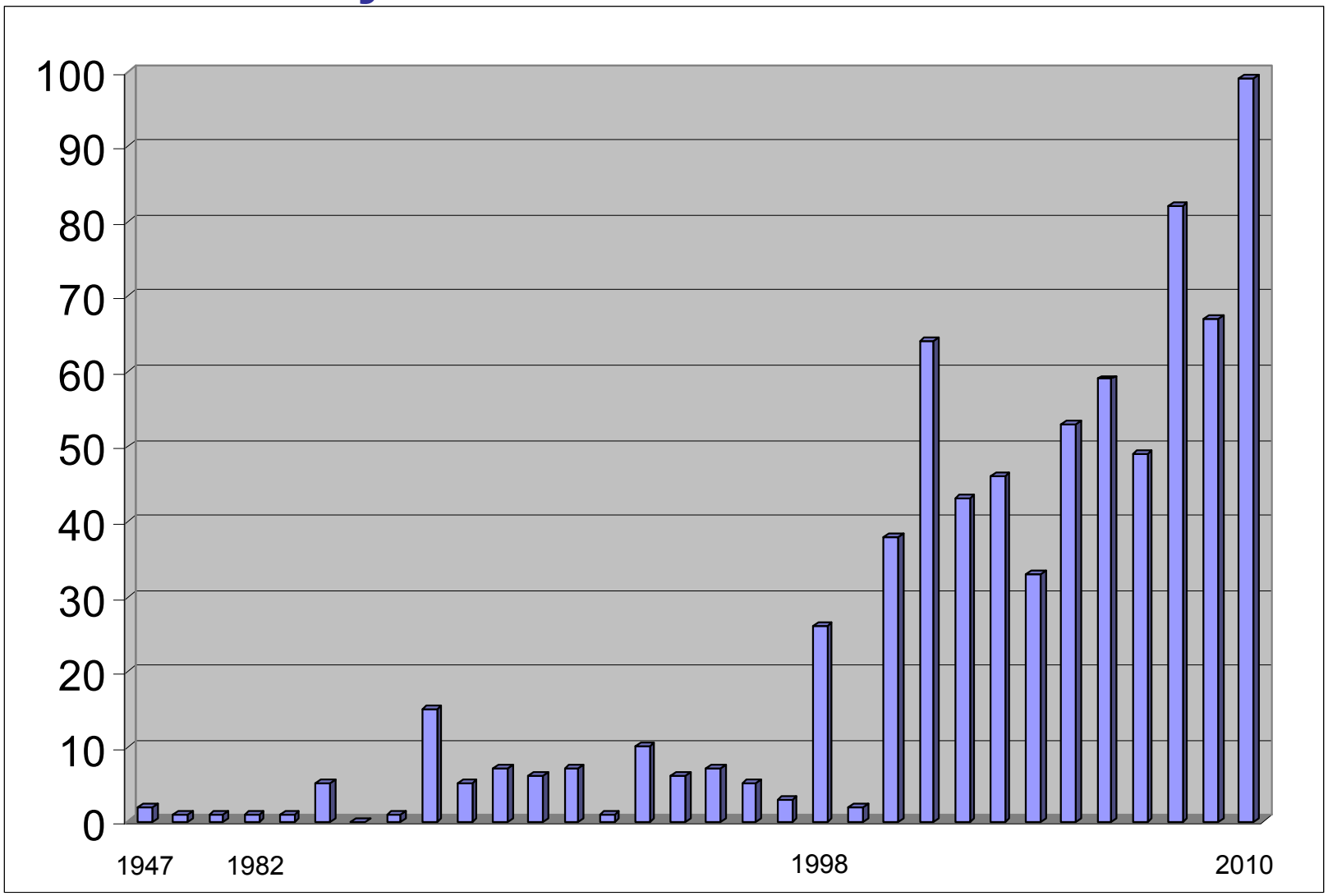
Calabrese, 2007, A dose of common sense. Good Clinical Practice Journal, July, pp12-16

A - Low-dose stimulation high-dose inhibition

B - Low-dose inhibition high-dose stimulation

- **Confined to biochemistry, radiation biology and toxicology**

Publications Citing “Hormesis” in PubMed Dramatically Increased from 1947 to 2010



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Hormesis
Current experience based on the literature

Biphasic dose-response curves are not only confined to biochemistry, radiation biology and toxicology, but extend across many areas of biomedical science and clinical medicine

- "including anxiety, seizure, memory, stroke, cancer chemotherapy, dermatological processes such as hair growth, osteoporosis, ocular diseases, including retinal detachment, statin effects on cardiovascular function and tumor development, benign prostate enlargement, male sexual behaviors/dysfunctions, and prion diseases."

  Calabrese, 2008, Br J Clin Pharm 66:594-617

- Neuroscience and Hormesis – Four special issues covering neuronal survival, neurite outgrowth, glial adaptive responses to neurotoxins, p-glycoprotein efflux transporter activity, anxiolytic drugs, traumatic brain injury, stroke, addiction, Alzheimer's Disease ….

  Critical Reviews in Toxicology, 2008, Volume 38, Nos 4 – 7

- Aging, chemosensitization, oxidative stress, caloric restriction, cancer, memory and synaptic plasticity, drug binding, risk of stroke, cellular response (biochemical and physiological) ….

  American Journal of Pharmacology and Toxicology, 2008, Volume 3, Issue 1

- Cellular stress, exercise physiology, homeopathy, fish biology, scoliosis, migraine, nanoparticles

  PubMed, 2009, 2010

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Hormesis: Implications for the Pharmaceutical Industry

Hormesis:- beyond toxicology ….. impacts efficacy

- Numerous examples across biomedical science and clinical medicine in the literature

Drug Research & Development

- Do not assume only linear, sigmoidal or threshold dose-response relationships for safety and/or efficacy

- Need to study a large range of concentrations/doses with increased sampling to fully and accurately characterize the shape of the concentration/dose-response curves

Challenges for the Pharmaceutical Industry

- Lack of preclinical systems that accurately predict clinical outcome
  - **toxicity**
  - **therapeutic efficacy**
- High failure rate at all stages of research and development (R&D)
  - **How many projects have been stopped because of**
    - Inappropriate target - Discovery
    - Toxicity - Preclinical
    - Lack of efficacy - Clinical
- Longer timelines from bench-to-bedside
- Ever increasing costs
- Increasing complexity of testing and developing molecularly targeted drugs/biologics and advanced technologies
- Increasing hurdles of regulatory agencies and payers

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Challenges for the Pharmaceutical Industry
Common Failures in Drug Development

- Poor protocol
  - Lack of an appropriate control group
  - Inappropriate or unspecified endpoints
  - Inappropriate or unspecified statistical analysis
    - Detecting statistical, but not clinical significance
    - Biomarker ≠ Surrogate endpoint
- Inaccurate dose selection
- Inappropriate selection of target population
- Incorrect length and timing of study
- Unrepresentative sampling with high attrition rates

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Challenges for the Pharmaceutical Industry
Common Failures in Drug Development

Inaccurate dose selection

- "*What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects.*" (ICH-E4 November 1994)
- Minimum effective dose and maximum useful dose
- Choice of a starting dose might be affected by
  - intersubject variability in PD response to a given blood concentration level
  - Intersubject PK differences
    - **Non linear kinetics**
    - **Metabolic polymorphism**
    - **Drug-drug interactions**

Start low and go slow

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Challenges for the Pharmaceutical Industry
Common Failures in Drug Development

Inappropriate selection of target population

- Identify early factors that could lead to differences in PK of drugs among individuals
  - Gender, race
  - Other diseases (renal or hepatic failure)
  - Diet (fasted or fed)
  - Concurrent therapies (drug-drug interactions)
  - Phenotype (age, weight)

Challenges for the Pharmaceutical Industry
Common Failures in Drug Development

Incorrect length and timing of the study

- Identify the time needed to detect (favorable and undesirable) drug effects (temporal hormesis)

- Dose interval is too long compared to the half-life of the drug
  - Use PD basis for choosing the dose interval and for adverse events associated with blood peak levels
  - Peak and trough blood levels and their relationship could influence the dose interval chosen

- Dose-response could be different in morning versus evening
  - Fasted versus fed
  - Related to cumulative dose, rather than daily dose
  - Duration of exposure (e.g., tachyphylaxis, tolerance)

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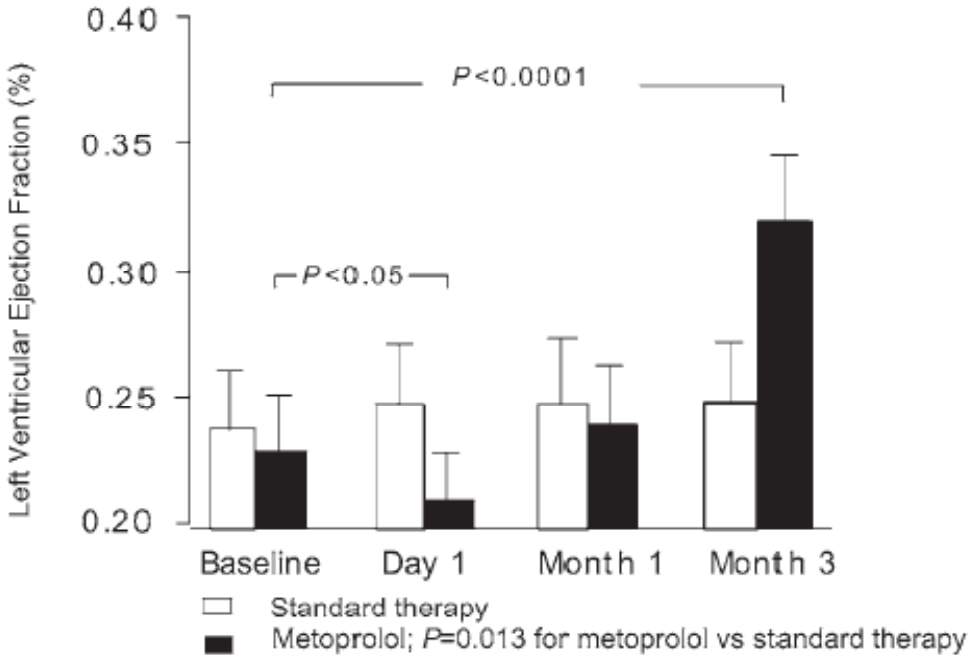
Negative acute effect of metoprolol on measure of chronic heart failure replaced by beneficial effects with chronic administration



- Changes in left ventricular ejection fraction (echocardiography)
  - from baseline to day 1, month 1 and month 3
  - in metoprolol and standard therapy groups
- Standard therapy
  - long term angiotensin converting enzyme inhibitor
  - except 2 patients who received isosorbide dinitrate / hydralazine
- Ejection fraction
  - Decreased about 25% on day 1
  - Increased only after 1 month
  - By 3rd month patients showed significant increase in left ventricular ejection fraction

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Dudekula et al., Dose Response 2005;3:414-424

Challenges for the Pharmaceutical Industry
Common Failures in Drug Development

Unrepresentative sampling with high attrition rates

- Most side-effects of drugs occur early and may disappear with continued treatment
  - Can result in higher rate of undesirable effects at lower doses
- Patients are sometimes titrated to the desired response and those patients relatively unresponsive are more likely to receive a higher dose giving an apparent, but mis-leading inverted “U-shaped” (hormetic) dose-response curve
  - If PK screening is done obtaining drug concentrations, a relationship of effects (desirable and undesirable) to blood concentrations may be discerned

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Challenges in the Pharmaceutical Industry
Impact of hormesis: Some Solutions

- Preclinical
  - Microdosing/Phase 0
- Phase I
  - Pharmacometrics
- Phase II/III
  - Adaptive trial design

Challenges in the Pharmaceutical Industry - Impact of hormesis
Some Solutions – Microdosing in Phase 0

Microdosing (EU) or Phase 0 (US)

- Aims to reduce resources (i) non-viable drugs and (ii) animal testing
- Studies drug behavior in humans at ultra-low (100 µg) doses unlikely to produce whole-body effects, but allows the study of cellular response (efficacy and toxicity)
- Helps predict whether a drug is viable for phase I testing

"*Microdosing addresses*

- ethical problems of administering full human doses of a drug or biologic to healthy volunteers, based only on available animal and in vitro data,
- the extreme inaccuracy of predicting humans doses based on animal data, as has been the standard procedure until now." Graul, 2008, Drug News Perspect 21:36-43

" *…a better understanding is needed for those properties of a drug that might lead to significant nonlinearities in the pharmacokinetics seen between a microdose and a therapeutic dose.*"

Lappin and Garner, 2008, Expert Opin Drug Metab Toxicol 4:1499-1506

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Challenges in the Pharmaceutical Industry - Impact of hormesis
Some Solutions – Pharmacometrics in Phase I

Pharmacometrics

- An emerging science
  - Quantifies drug, disease and clinical trial information (development)
  - Aid efficient drug development and/or regulatory decisions
  - Focus on drug models for concentration effect, dose-response, PKPD
    - **PK (exposure)**
    - **PD (response)**
    - **Desired and undesired effects**
    - **Individual patient characteristics**

- The single-most important strength of such analyses is
  - Its ability to integrate knowledge across the development program, compounds, and biology
  - Dose-response data should be explored for possible differences in subsets based on demographic characteristics, such as age, gender, or race

Challenges in the Pharmaceutical Industry - Impact of hormesis
Some Solutions – Adaptive Trial Design in Phase II/III

Adaptive Trial Design (ATD)

- ATD is defined as a study that includes a sequence of interim analyses to enable modification of the course of the clinical trial dynamically (e.g., used by DMCs to stop trials early due to overwhelming evidence of efficacy)

- Possible adaptation (by dropping/adding treatment arms) of clinical trials
  - Biomarker-adaptive design
  - Drop-loser design
  - Sample size re-estimation

- Complexity of an adaptive trial is higher than a traditional trial, but it
  - permits multiple objectives to be addressed in a single trial
    - **identifying the dose-range as well as the patient population likely to get the maximum drug benefit**
  - potentially reducing the overall costs

Phillips and Du Mond, Pharmaceutical Executive July 2007, Vol 5, Iss 5

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Guideline for Industry
Dose-Response Information to Support Drug Registration

"This guideline was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at Step 4 of the ICH process, March 10, 1994. At Step 4 of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and the USA."

ICH-E4 November 1994

FDA Guideline for Industry
Dose-Response Information to Support Drug Registration

Purpose of dose-response information

- ”Knowledge of the relationships among dose, drug concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help ….”
  - Identify an appropriate starting dose and titration steps
  - Establish a therapeutic index (safety and efficacy … benefit/risk)
  - Prepare dosage and administration instructions for labeling
  - Multiple regulatory agencies to make approval decisions

FDA Guideline for Industry
Dose-Response Information to Support Drug Registration

Study Designs for Assessing Dose-Response (1/3)

- Study design and population selection based on
  - Phase of development
  - Therapeutic indication
  - Severity of disease
  - **Potential for non-linear, sigmoidal, threshold, hormetic PK/PD**
  - May reduce the number of failed phase III trials

- Compare several doses versus fixed single doses
  - Can use PK data to ensure optimal dose spread
    - **Where PK variability is high, can used doses further apart**
    - **Ensure testing wide range of doses to determine optimal patient safety and clinically meaningfulness**
    - **Especially important when there is no biomarker/surrogate enpoint**

FDA Guideline for Industry
Dose-Response Information to Support Drug Registration

Study Designs for Assessing Dose-Response (2/3)

- Parallel dose-response
  - Widely used randomization to several fixed-dose groups
  - If study includes a parallel placebo then an absolute drug effect can be obtained
    - **Low dose must be significantly different in clinical response to be recommended**
    - **Without placebo, a positive slope indicates a drug effect**
  - Provides population average (mean) and not individual dose-response curves
  - Protects against missing an effective dose due to hormetic dose-response (e.g., with mixed antagonist/agonist)

- Cross-over dose-response
  - Uses several doses in the same patient – randomized multiple cross-over of different doses
  - Patients need to return to baseline after treatment cessation and responses not irreversible, but disease is stable (e.g., blood pressure)
  - Can be long duration for individual patients to avoid carry-over effects
  - But analytic problems with treatment withdrawals, uncertainly about carry-over effects

FDA Guideline for Industry
Dose-Response Information to Support Drug Registration

Study Designs for Assessing Dose-Response (3/3)

- Forced titration
  - All patients receive rising doses
    - **similar to cross-over but assignment of dose is ordered and not random**
  - Controlled with parallel placebo
    - **allows series of comparisons as parallel fixed-dose trial**
  - Compared with parallel fixed-dose study
    - **Fewer patients, wide range of doses**
  - Cannot determine response due to increased dose versus response to increased time on drug or cumulative drug dose effect
  - Design gives poor information on AEs, and little room to show better effect at higher doses
  - With placebo can provide clear evidence for effectiveness and help choosing doses
  - Can give population-average and individual (with low time-dependent drug effect) DR

- Placebo-controlled titration to endpoint
  - Uses several doses in the same patient
  - For use with prompt, non-irreversible responses (e.g., cardiac arrhythmia)
  - Could give misleading hormetic response if there are poor responders who are titrated to high doses
    - **But sophisticated statistical analysis can correct by modeling populattion and individual dose-response**
  - Could risk confounding of time and dose effects
    - **But could be used as an early study to find doses for a definitive parallel study**

Post-approval dose adjustments by the FDA

- 1 in 5 drugs approved by the FDA between 1980 and 1999 had dosage adjustments post-approval
  - 20% of these had the dose increased
  - 80% of these had the dose decreased
- Following the guidelines more closely may lead to fewer post-approval adjustments

Cross et al., 2002, Post-marketing drug dosage changes of 499 FDA-approved new molecular entities, 1980 – 1999 Pharmacoepidemiology and Drug Safety, 11:439-446

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Take Home Messages (1/2)

More thorough dose-response data are needed for all (new) molecular entities and these data should

- avoid the bias assuming that the dose-response relationship is linear/sigmoid
- plan studies using several concentrations/doses
- employ (clinical) study designs to elucidate maximum PK/PD information
- be explored for differences in data subsets, eg, demographics, diseases, drugs
- emphasize elucidation of the full dose-response
- be obtained from the entire database of concentration/dose-response data

Attention should be paid not only to the shape of the typical individual's or population's (group average) dose-response curve, but also the time (temporal hormesis) needed to detect a change in the effect (desirable/undesirable)

Endpoints (efficacy and safety) selected may change along the development process and

- it should not be assumed that concentration/dose-response relationships will be similar in shape and maintained across different endpoints

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Take Home Messages (2/2)

- Dose-response data for both beneficial and undesirable effects may
  - provide information that allow approval of a range of doses, assuming an appropriate benefit-risk
- Conducting thorough concentration/dose-response studies early in development could prevent
  - failed later stage clinical studies due to
    - inability to detect hormetic dose-response curves and thereby
    - acquire databases with ineffective or excessive doses
- Sponsors and regulatory agencies should be open to validated but novel analytical techniques and clinical trial designs to obtain optimal concentration/dose-response data,
  - but these approaches should not be used as a way to avoid the requirement for dose-response data from a prospective, randomised multi-dose-level clinical trial

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Concluding Remarks (1/2)

Safety

- **Hormesis challenges our mindset about toxic concentrations and doses**

Efficacy

- **Hormesis extend across many areas of biomedical science and clinical medicine**
- **Provide more robust data moving forward in a therapeutic area**

Resources

- **Validation and targeted use of existing tools and techniques can help to ensure that drugs with improved benefit/risk profiles do not necessarily add more to the cost of drug R&D**

Re-examination of past failures

- **It is possible that development was stopped in some areas not because the target was incorrect or the mechanism was invalid, but simply because we chose the wrong dose assuming a linear or threshold dose-response relationship**

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Concluding Remarks (2/2)

Drug R&D is about science, medicine and creating drugs to help patients. Consequently, the impact of hormesis on pharma also applies to academic and basic research

- Elucidation of basic mechanisms of action underlying hormesis

If we want to have an impact on ways of working, so that science is conducted with the concept of hormesis considered as mainstream, we must continue to:

- Provide convincing examples in basic science and clinical medicine, addressing mechanisms of action, and in drug discovery and development
- Illustrate beneficial/detrimental effects of our understanding of basic science and clinical medicine based on hormesis

Thank you

for your attention, questions and remarks

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