Value-Driven Drug Development

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Patient-Centric Product Design, Drug Development, and Manufacturing
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1750 Rockville Pike, Rockville, MD 20852 USA

TRACK #2 EMERGING TECHNOLOGIES AND PATIENT CENTRICITY IN EARLY DRUG DEVELOPMENT
SESSION 2: DESIGNING FOR DELIVERY: DRUG DISCOVERY AND THE EARLY DEVELOPMENT INTERFACE
Moderator: *Diane Paskiet, West Pharmaceutical Services*

Disclaimer

The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA.

With Special Thanks!

Dr. Wenny Du, MS, PhD
Deputy Director CMC, Global Regulatory Affairs at Bayer HealthCare

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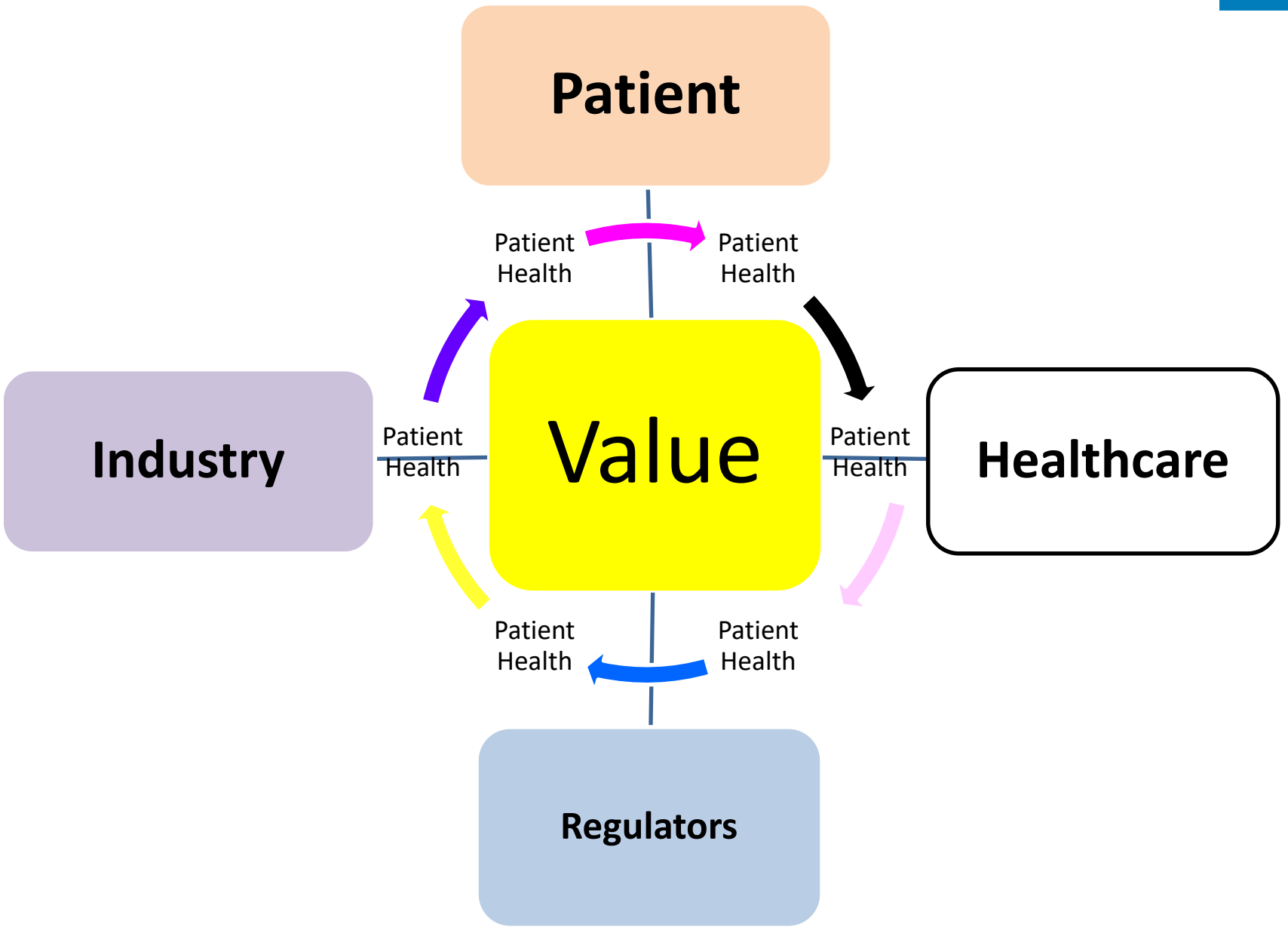
Regulatory Research Manager at Perrigo Company plc

Value

- *noun* The regard that something is held to deserve; the importance, worth, or usefulness of something.
  - *'your support is of great value'*

Common Values



The Value of Planning; Planning for Value

"Give me six hours to chop down a tree and I will spend the first four sharpening the axe."
– Abraham Lincoln

"If you don't know where you are going, you'll end up someplace else."
– Yogi Berra

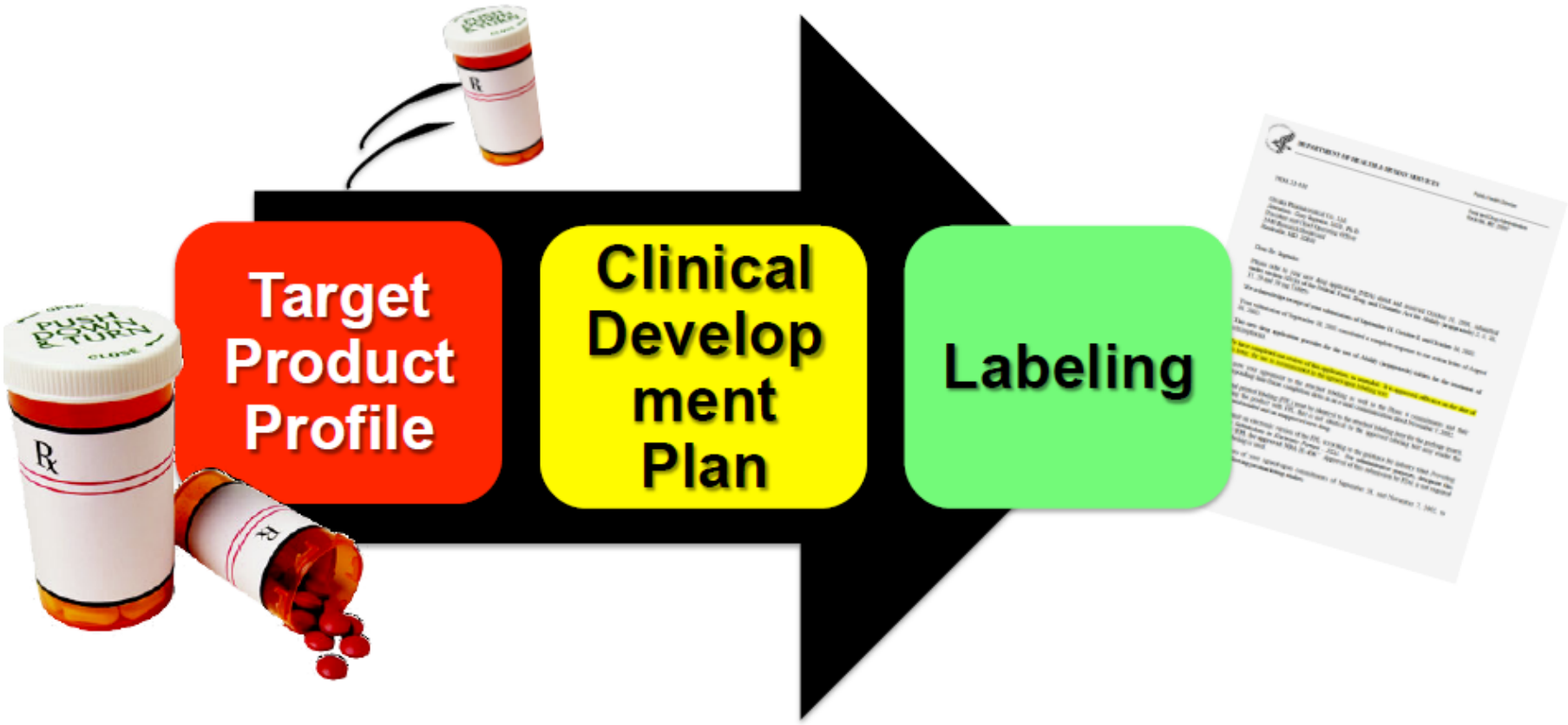
IT TAKES AS MUCH ENERGY TO WISH AS IT DOES TO PLAN.

- ELEANOR ROOSEVELT -

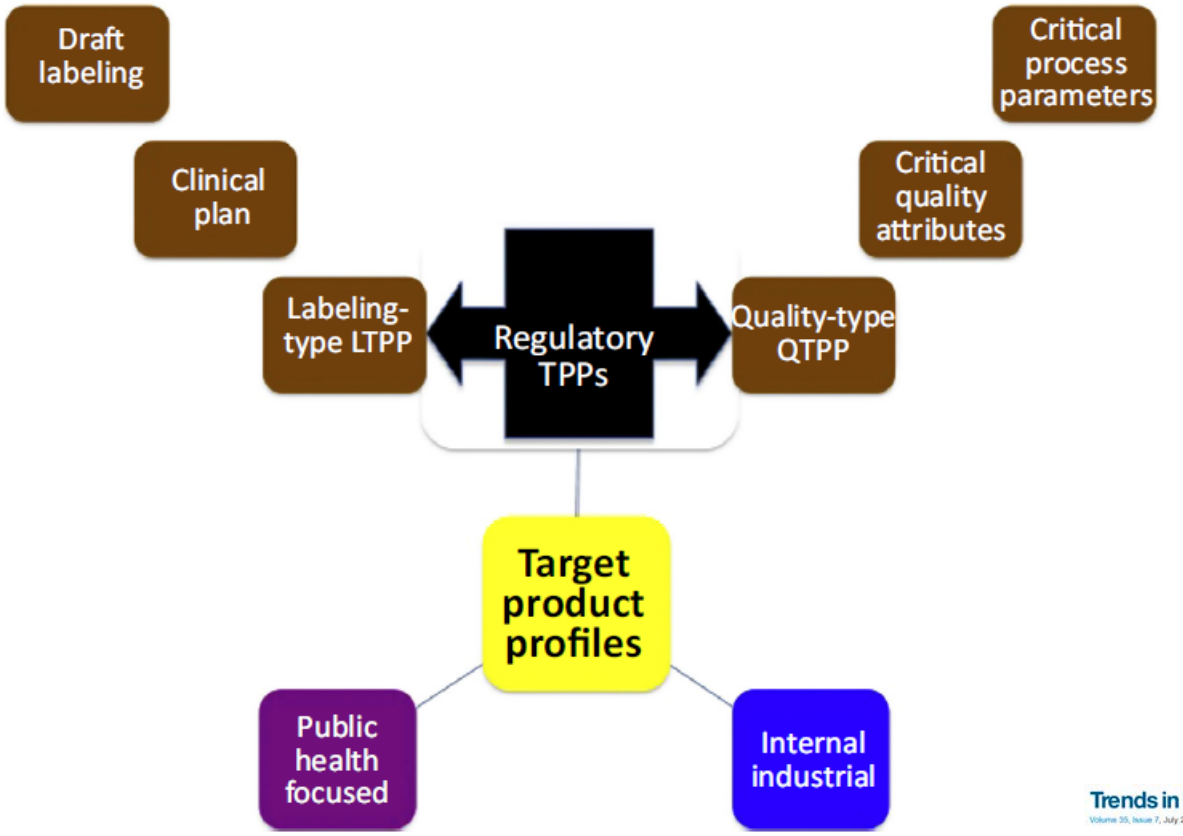
"Plans are of little importance, but planning is essential."
– Winston Churchill

It is sometimes not so important what you think, but that you think about it.

Developing a Clinical Development Strategy



Multiple Faces of the Target Product Profile



Trends in Biotechnology

What's the Regulatory Value of a Target Product Profile?

Guidances and Literature on Target Product Profiles and Associated Topics

Quality by Design for ANDAs:
An Example for
Immediate-Release Dosage Forms

Introduction to the Example

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current *Step 4* version
dated August 2009

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Guidance for Industry

Q8, Q9, & Q10
Questions and Answers

Appendix
Q&As from Training Sessions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2012
ICH

Review Article

Understanding Pharmaceutical Quality by Design

Lawrence X. Yu, Gregory Amidon, Mansoor A. Khan, Stephen W. Hoag, James Polli, G. K. Raju and Janet Woodcock

INTRODUCTION

PHARMACEUTICAL QUALITY BY DESIGN OBJECTIVES

Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

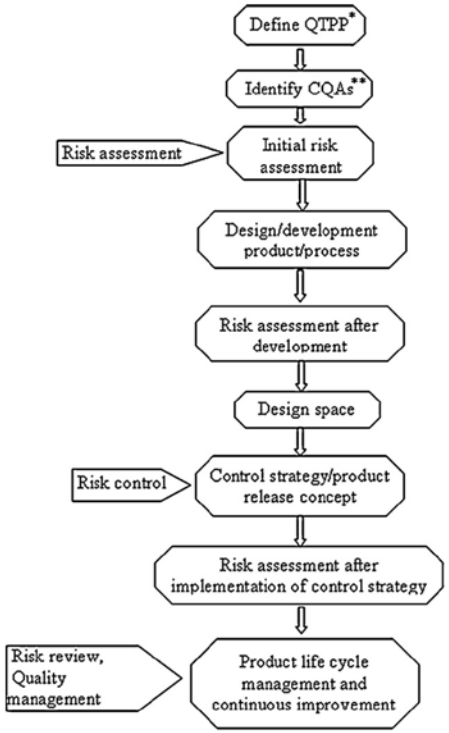
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2007
Procedural

Sample of the QTPP



*QTPP-Quality target product profile
**CQAs-Critical quality attributes

TPP and QTPP for a generic dispersible tablet dosage form.

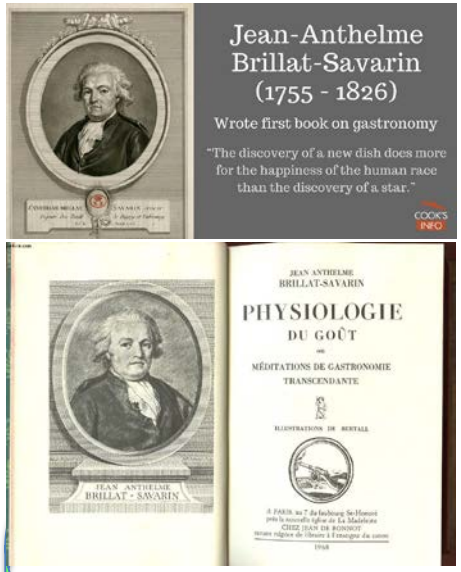
Attribute	QTPP		Criticality
	TPP	TPQP	
Dosage form	Dispersible tablet	DT (<3 min), dissolution (not less than 85%(Q) in 30 min in pH 6.8 buffer medium)	Ensures complete dispersion, release of drug, efficacy and ease of administration
Appearance	Uncoated tablets	IR round tablets	Patient acceptability and compliance
Strength	46.5 mg	Identification (positive), Assay (±5%), content uniformity (complies)	Efficacy
Route of administration	Oral	Palatable	Patient compliance to therapy
Proposed indications	Treatment of pain associated with arthritis	Dissolution and bioequivalence	Ensure therapeutic efficacy
Impurities	–	Qualified to meet ICH Q3B and Q6A criteria	Safety is assured by controlling any impurity at NMT 0.2% and total impurities at NMT 0.5%. Limit has been qualified in toxicological studies.


International Journal of Pharmaceutics

Quality by design approach for formulation development: A case study of dispersible tablets

[INSERT STORY HERE]

A History of Multi-Attribute Optimization



"The Physiology of Taste"

CORNELL UNIVERSITY
DAIRY SCIENCE

TABLE 2. 'Standardized Sensory Language' for the Quantitative Description of Vanilla Ice-creams. Flavor References for Vanillin, Caramel, Whey-like and Phenolic were only Smelled During the Language Familiarization Sessions.

Manual firmness	Definition: mechanical textural attribute relating to the force required to achieve a given deformation or penetration of a product. Procedure: manual force required to cut with a standardized spatula horizontally through the ice-cream middle section. Spatula size: thickness: 1 mm, width: 7 mm; ice-cream volume: 40 ml; testing temperature between −7 and −12°C, depending on ice-cream composition. High reference standard (a): cooking butter, 82% fat, Bura AG, Switzerland; 4°C. Low reference standard (b): margarine, 40% fat, Delice Mabona Minarine Brand, Migros Supermarket, Switzerland; 4°C. b a
Cold sensation	Definition: thermal cooling sensation given by the sample on the tongue and palate during the ice-cream melting phase. Not to be confused with the trigeminal cooling of menthol. Procedure: by putting a whole spoon (side with sample facing the tongue) of ice-cream in the mouth, between tongue and palate, evaluate this sensation while the sample is melting. High reference standard: ice cubes (*c.* 10 ml volume).
Ice crystal	Definition: presence of ice crystals in the sample. The smoother the sample, the less (or the smaller) ice crystals are perceived. Procedure: by putting a whole spoon (side with sample facing the tongue) of ice-cream in the mouth, between tongue and palate, evaluate this sensation right after the sample is placed in the mouth. High reference standard (a): sample 3 × 8 × 12; −7°C. Low reference standard (b): sample 3 × 8 × 20; −10°C.

a

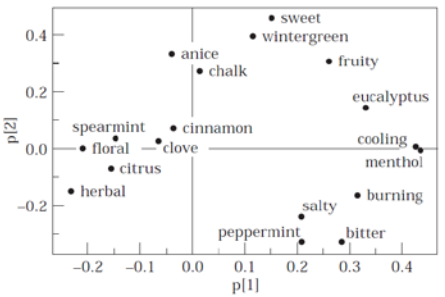


Fig. 1 Principal component analysis of the South American flavour space. Attribute loading for principal components one (p[1]) and two (p[2]), which explained 43.3% of the variance

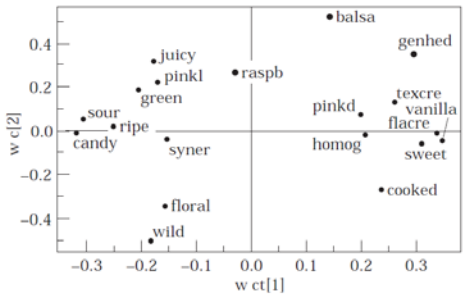
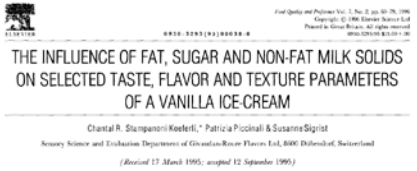


Fig. 5 PLS regression analysis (55.4% (X), 81.4% (Y) of consumer acceptance data on sensory analytical data from flavour profiling, with genhed = general preference

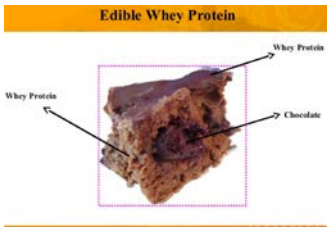


THE INFLUENCE OF FAT, SUGAR AND NON-FAT MILK SOLIDS ON SELECTED TASTE, FLAVOR AND TEXTURE PARAMETERS OF A VANILLA ICE-CREAM

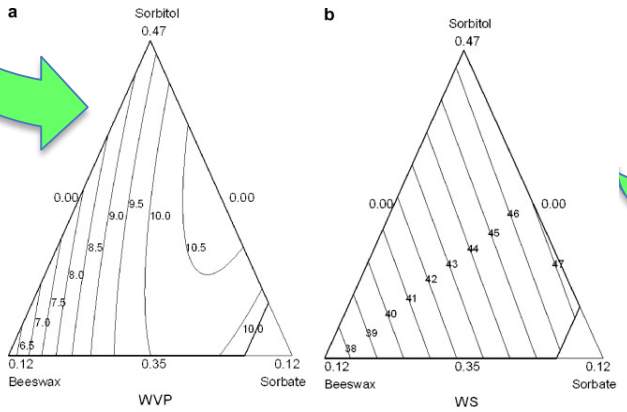
Chantal R. Stampanoni Koelliker,* Patrizia Piccinali & Susanne Sigrist
Sensory Science and Evaluation Department of Givaudan-Roure Flavors Ltd, 8600 Dübendorf, Switzerland

(Received 17 March 1995; accepted 12 September 1995)

Optimization in the Real World



…**Control of surface moisture content** can significantly **reduce the growth of microorganisms** and the rate of **deteriorative reactions**, thereby **increasing the storage stability of foods** (Kester and Fennema, 1986)…Edible films and coatings with good water and/or oxygen barrier properties are usually not adequate by themselves to retard microbial growth. Therefore, **the incorporation of antimicrobial agents** into edible coating formulations is needed to obtain stronger inhibitory effect against microbial growth



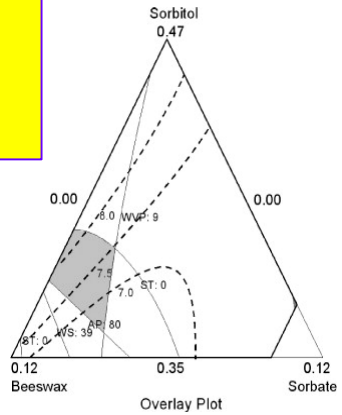
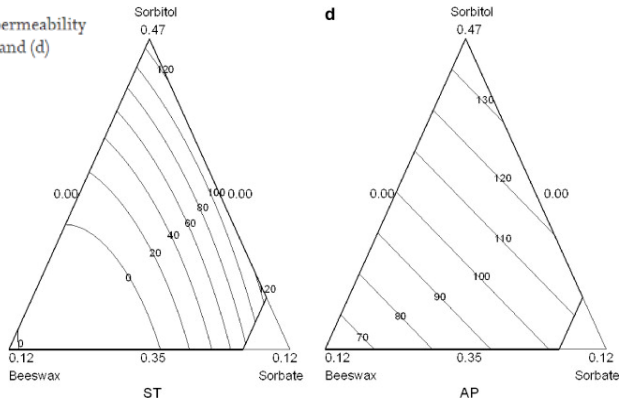


Fig. 6. Optimum region obtained by superimposing contour plots of all four responses generated at 53.3% protein concentration. Shaded area represents optimum region with minimum stickiness, WVP ⩽ 9 g mm m^{-2} h^{-1} kPa^{-1}, WS ⩾ 39% and AP ⩾ 80. Dashed lines show the change in potassium sorbate diffusivity (10^{-11} m^2 s^{-1}).

Fig. 5. Computer generated mixture contour plots for (a) water vapor permeability (g mm m^{-2} h^{-1} kPa^{-1}); (b) water solubility (% dry matter); (c) stickiness and (d) appearance at 53.3% protein concentration.




Journal of Food Engineering

Optimization of edible whey protein films containing preservatives for water vapor permeability, water solubility and sensory characteristics

Process Analytical Technology

Table 1. Quality target product profile (QTPP) for the pH-independent controlled release matrix tablet.

QTPP element	Target
Dosage form	Controlled release monolithic matrix tablet
Route of administration	Oral
Dosage strength	80 mg
Stability	Should be stable at least 6-month shelf life at long term stability conditions
Physical properties	Should have sufficient hardness to be resistant to transportation
Dissolution	pH independent controlled release for 12 h

Table 2. Critical quality attributes (CQAs) of the pH-independent controlled release matrix tablet.

CQAs	Target	Justification of criticality
Assay	80 mg ± 5.0 %	The minimum dose to achieve pharmacological effect for Valsartan is 80 mg. Must meet compendia standards
Hardness	Min 40 N	Hardness has impact on friability, dissolution, and bioavailability
Dissolution	In vitro dissolution at 2nd hour in acidic medium (0.1N HCl) should be more than 20 % and in vitro dissolution at 8th hour in basic medium (pH 6.8 phosphate buffer) should be more than 85 % for maintenance of bioavailability higher than commercial pH dependent IR dosage form	Dissolution is significantly effective on bioavailability of solid dosage forms

Table 3. Risk assessment of critical material attributes (CMAs) on drug product CQAs, with control strategies.

	Formulation variables				
Drug Product CQAs	pH modifier type	pH Modifier level	Filler type	Polymer type	Solubility enhancer level
Assay	Low	Low	Low	Low	Low
Dissolution	High Type should be identified and fixed by OFAT	High Level range should be identified and fixed within DoE design space	High Type should be identified and fixed by OFAT	High Type should be identified and fixed by OFAT	High Level range should be identified and fixed within DoE design space
Chemical stability	Low	Medium Chemical Stability should be identified with compatibility and stability study	Low	Low	Medium Chemical Stability should be identified with compatibility and stability study

Relative risk ranking: Low risk: no further investigation is needed.; Medium risk: further investigation may be needed.; High risk: the further investigation is needed.

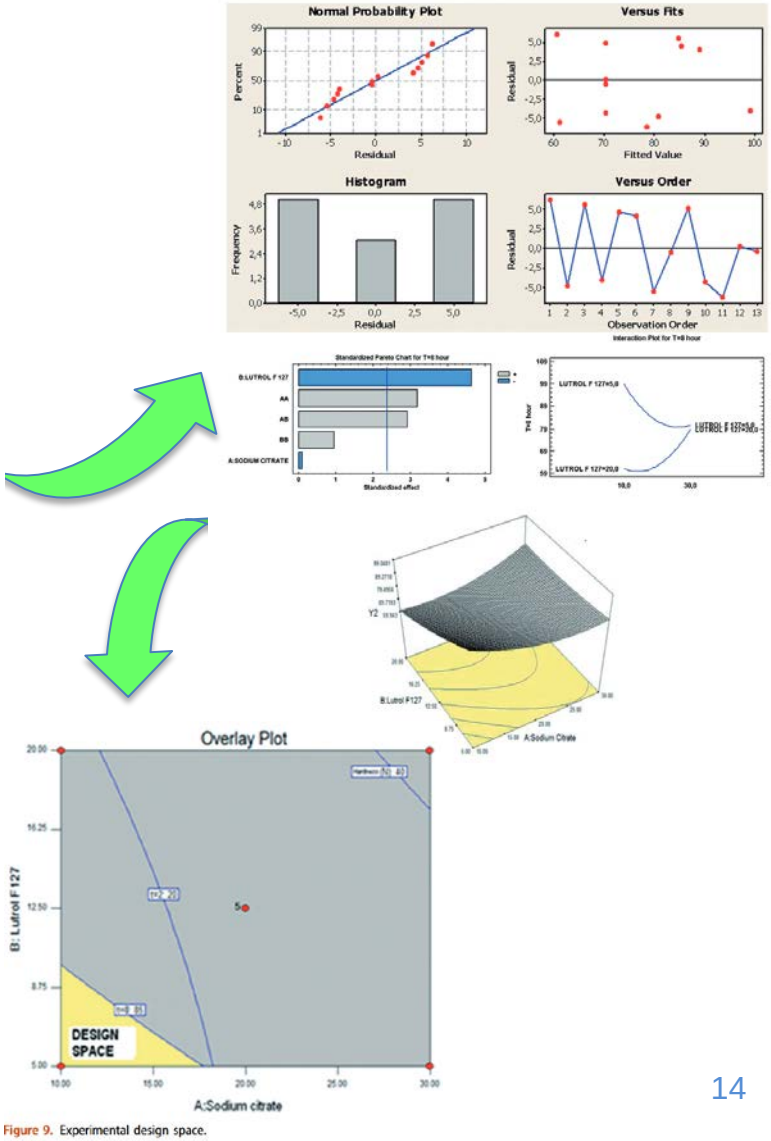


Figure 9. Experimental design space.

Mehtap Saydam & Sevgi Takka (2018) Development and *in vitro* evaluation of pH-independent release matrix tablet of weakly acidic drug valsartan using quality by design tools, Drug Development and Industrial Pharmacy, 44:12, 1905-1917, DOI: 10.1080/03639045.2018.1496450

Benefits of 'Quality by Design'

Survey Topics

• Elements of QbD
  - Does the company apply elements of QbD?
  - What business units apply QbD, i.e., new/legacy products; R&D/manufacturing?
• Drivers for QbD, i.e., regulatory, management, other?
• Benefits of QbD, including metrics and possible examples, i.e., regulatory flexibility, cost reduction?
• Additional level of resources and cultural changes to achieve QbD
• Regulatory flexibility, i.e., experiences from QbD interactions/filings
• QbD for in-licensed products and third party manufacturers
• Use of modelling in QbD
• Regulatory response to modelling
• PAT tools to support QbD
• Desired sensor technology
• Future of QbD in your company (interviewees opinion)

Table A. Survey Topics.

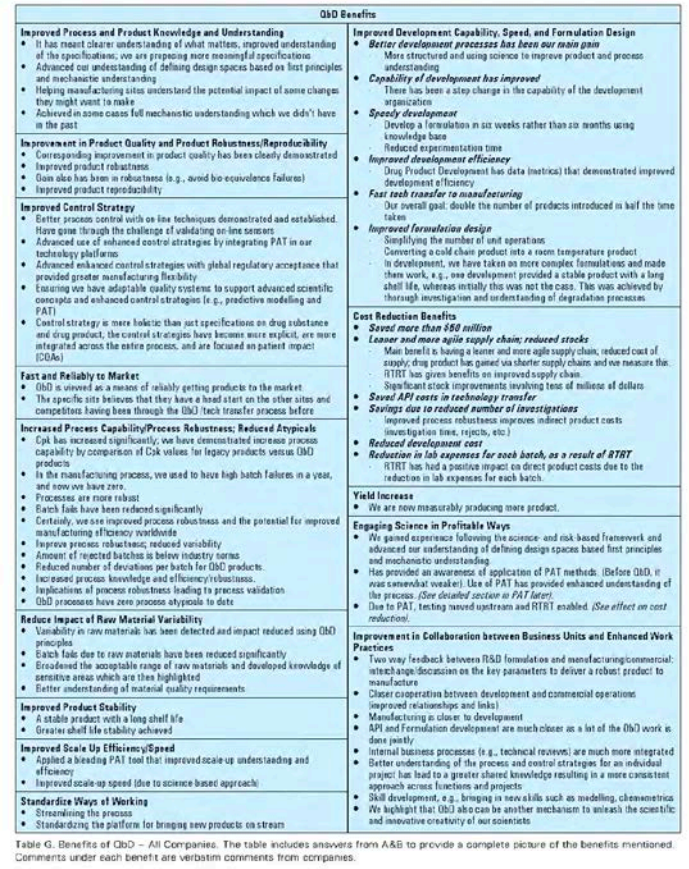
Companies in the Survey
1. Abbott (USA)
2. AstraZeneca (UK)
3. Bristol Myers Squibb (UK and USA)
4. GSK (USA)
5. Jazz Pharmaceuticals Inc. (USA)
6. Eli Lilly and Company (USA)
7. Merck (USA and Ireland)
8. Pfizer (USA, 2)
9. Centocor Biologics (J&J) (Ireland)
10. Vertex Pharmaceuticals (USA)
11. United Therapeutics Inc (USA)

Table B. Companies Interviewed that Perform Elements of QbD. Where there are two locations mentioned it indicates that we received a completed questionnaire from each location; from one company we received two completed questionnaires from different groups in the USA (14 questionnaires in total).

QbD Benefits
Company A
Benefits from Cost Savings • Saved more than $60 million • QbD processes have "zero process atypicals" to date • Saved API costs in technology transfer • Advanced enhanced control strategies with global regulatory ac that provided greater manufacturing flexibility
Benefits in Process Understanding • Greater process understanding and greater assurance of produc • We gained experience following the science- and risk-based frar and advanced our understanding of defining design spaces base principles and mechanistic understanding. • Advanced use of enhanced control strategies by integrating PA technology platforms.
Benefits in Work Practices • Manufacturing is closer to development • Improved internal business processes (e.g., technical reviews ar more integrated) • API and Formulation Development are much closer as a lot of th work is done jointly • Ensuring we have adaptable quality systems to support advanc scientific concepts and enhanced control strategies (e.g., predic modelling and PAT) • We highlight that QbD also can be another mechanism to unleas scientific and innovative creativity of our scientists
Company B
Benefits from Cost Savings • QbD processes have "zero process atypicals; we used to have p with high batch failures in a year" • Improved product quality • Improved product robustness • A stable product with a long shelf life

Benefits in Process Understanding
• Greater process understanding
• Improved formulation design:
  - Simplifying the number of unit operations.
  - In development, we have taken on more complex formulations and made them work (e.g., one development provided a stable product with a long shelf life, whereas initially this was not the case). This was achieved by thorough investigation and understanding of the processes involved.

Table F. Benefits of QbD – Companies A&B.



QbD Benefits

Improved Process and Product Knowledge and Understanding
- It has meant clearer understanding of what matters, improved understanding of the specifications; we are proposing more meaningful specifications
- Advanced our understanding of defining design spaces based on first principles and mechanistic understanding
- Helping manufacturing sites understand the potential impact of some changes they might want to make
- Achieved in some cases full mechanistic understanding which we didn't have in the past

Improvement in Product Quality and Product Robustness/Reproducibility
- Corresponding improvement in product quality has been clearly demonstrated
- Improved product robustness
- Gain also has been in robustness (e.g., avoid bio-equivalence failures)
- Improved product reproducibility

Improved Control Strategy
- Better process control with on-line techniques demonstrated and established. Have gone through the challenge of validating on-line sensors
- Advanced use of enhanced control strategies by integrating PAT in our technology platforms
- Advanced enhanced control strategies with global regulatory acceptance that provided greater manufacturing flexibility
- Ensuring we have adaptable quality systems to support advanced scientific concepts and enhanced control strategies (e.g., predictive modelling and PAT)
- Control strategy is more holistic than just specifications on drug substance and drug product, the control strategies have become more explicit, are more integrated across the entire process, and are focused on patient impact (CQAs)

Fast and Reliably to Market
- QbD is viewed as a means of reliably getting products to the market
- The specific site believes that they have a head start on the other sites and competitors having been through the QbD /tech transfer process before

Increased Process Capability/Process Robustness; Reduced Atypicals
- Cpk has increased significantly; we have demonstrated increase process capability by comparison of Cpk values for legacy products versus QbD products
- In the manufacturing process, we used to have high batch failures in a year, and now we have zero.
- Processes are more robust
- Batch fails have been reduced significantly
- Certainly, we see improved process robustness and the potential for improved manufacturing efficiency worldwide
- Improve process robustness; reduced variability
- Amount of rejected batches is below industry norms
- Reduced number of deviations per batch for QbD products.
- Increased process knowledge and efficiency/robustness.
- Implications of process robustness leading to process validation
- QbD processes have zero process atypicals to date

Reduce Impact of Raw Material Variability
- Variability in raw materials has been detected and impact reduced using QbD principles
- Batch fails due to raw materials have been reduced significantly
- Broadened the acceptable range of raw materials and developed knowledge of sensitive areas which are then highlighted
- Better understanding of material quality requirements

Improved Product Stability
- A stable product with a long shelf life
- Greater shelf life stability achieved

Improved Scale Up Efficiency/Speed
- Applied a bleeding PAT tool that improved scale-up understanding and efficiency
- Improved scale-up speed (due to science based approach)

Standardize Ways of Working
- Streamlining the process
- Standardizing the platform for bringing new products on stream

Improved Development Capability, Speed, and Formulation Design
- ***Better development processes has been our main gain***
  - More structured and using science to improve product and process understanding
- ***Capability of development has improved***
  - There has been a step change in the capability of the development organization
- ***Speedy development***
  - Develop a formulation in six weeks rather than six months using knowledge base
  - Reduced experimentation time
- ***Improved development efficiency***
  - Drug Product Development has data (metrics) that demonstrated improved development efficiency
- ***Fast tech transfer to manufacturing***
  - Our overall goal: double the number of products introduced in half the time taken
- ***Improved formulation design***
  - Simplifying the number of unit operations
  - Converting a cold chain product into a room temperature product
  - In development, we have taken on more complex formulations and made them work, e.g., one development provided a stable product with a long shelf life, whereas initially this was not the case. This was achieved by thorough investigation and understanding of degradation processes

Cost Reduction Benefits
- ***Saved more than $50 million***
- ***Leaner and more agile supply chain; reduced stocks***
  - Main benefit is having a leaner and more agile supply chain, reduced cost of supply; drug product has gained via shorter supply chains and we measure this. RTRT has given benefits on improved supply chain.
  - Significant stock improvements involving tens of millions of dollars
- ***Saved API costs in technology transfer***
- ***Savings due to reduced number of investigations***
  - Improved process robustness improves indirect product costs (investigation time, rejects, etc.)
- ***Reduced development cost***
- ***Reduction in lab expenses for each batch, as a result of RTRT***
  - RTRT has had a positive impact on direct product costs due to the reduction in lab expenses for each batch.

Yield Increase
- We are now measurably producing more product.

Engaging Science in Profitable Ways
- We gained experience following the science- and risk-based framework and advanced our understanding of defining design spaces based first principles and mechanistic understanding.
- Has provided an awareness of application of PAT methods. (Before QbD, it was somewhat weaker). Use of PAT has provided enhanced understanding of the process. *(See detailed section in PAT later).*
- Due to PAT, testing moved upstream and RTRT enabled. *(See effect on cost reduction).*

Improvement in Collaboration between Business Units and Enhanced Work Practices
- Two way feedback between R&D formulation and manufacturing/commercial; interchange/discussion on the key parameters to deliver a robust product to manufacture
- Closer cooperation between development and commercial operations (improved relationships and links)
- Manufacturing is closer to development
- API and Formulation development are much closer as a lot of the QbD work is done jointly
- Internal business processes (e.g., technical reviews) are much more integrated
- Better understanding of the process and control strategies for an individual project has lead to a greater shared knowledge resulting in a more consistent approach across functions and projects
- Skill development, e.g., bringing in new skills such as modelling, chemometrics
- We highlight that QbD also can be another mechanism to unleash the scientific and innovative creativity of our scientists

Table G. Benefits of QbD – All Companies. The table includes answers from A&B to provide a complete picture of the benefits mentioned. Comments under each benefit are verbatim comments from companies.

Kourti T, Davis B. The Business Benefit of Quality by Design (QbD). Pharm Eng Off Magazine of ISPE. 2012;32(4):1–10.

Making Use of Attributes

Target Product Profile Awakenol® for the Treatment of Sleeping in 410.651.82 Lectures

ATTRIBUTE	Gold Standard Dontsnuzenol®	[illegible]	[illegible] Case	High Case
Dosing and Formulation				
• Frequency	BID	BID	QD	[illegible]D
• Food Effect	Food effect - ↑ Cmax	No Food Effe[illegible]	[illegible]	[illegible]l Effect
• Capsule size	Size 1 capsule	Size 0 capsule		Size 2 capsule
• Formulation	Dry fill	Dry fill		Bead with IP advantage
Population				
	Adult, Children age 12-16	Adult, Children age 12-[illegible]	[illegible]dren Age 12-16	Adult, Elderly, Children Age 12-16
Efficacy				
• % Responders [1]	53	53	60	75
• Mean change in GPA	+ 0.04	+0.15	+0.25	+0.35
Safety				
• Warnings and Precautions	Black box warning for head spinning and hyperchloremia	Black box warning for head spinning and hyperchloremia	Warning for h[illegible] spinning or hyperchloren[illegible]	[illegible]g for either [illegible]nning or [illegible]loremia
Tolerability				
• Common (>5%) adverse events	• 10% Nausea • 07% Apathy • 05% Confusion	• 10% Nausea • 07% Apathy • 05% Confusion	• 1-2% less in key AEs	• Clinically significant reduction in key AEs • Reduction in AEs with Superior efficacy
Indications	Falling Asleep in 410.651.82	Falling Asleep in 410.651.82	+ Falling asleep in other JHU courses	+ Falling asleep in any University course

[1] % patients with a score of at least 85 on the Rockville Sleep Scale (RSS)

The low case may be the same or reasonably lower than the GS if there are other attributes in favor of your drug

You may not want any of a particular GS attribute, even in the low case

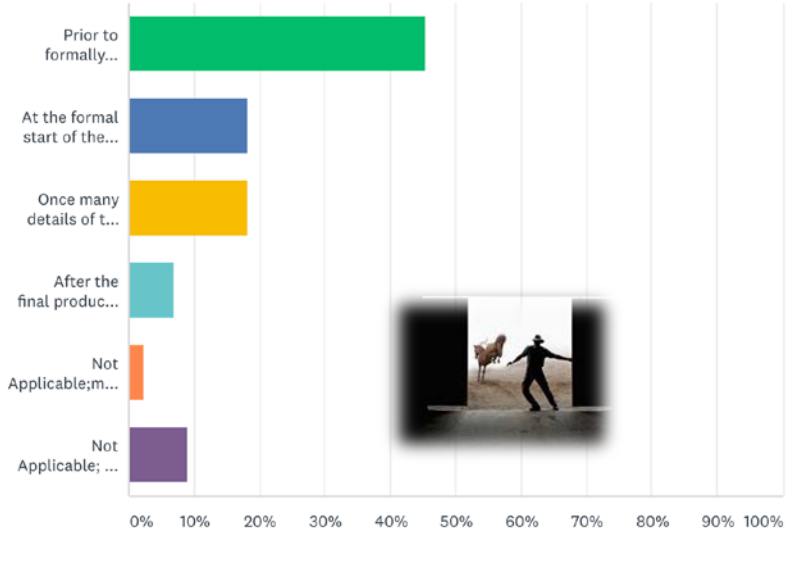
It is not uncommon to incorporate intellectual property positions in the TPP

Differences in numerical results are tricky to assign; be reasonable; What is clinically significant?

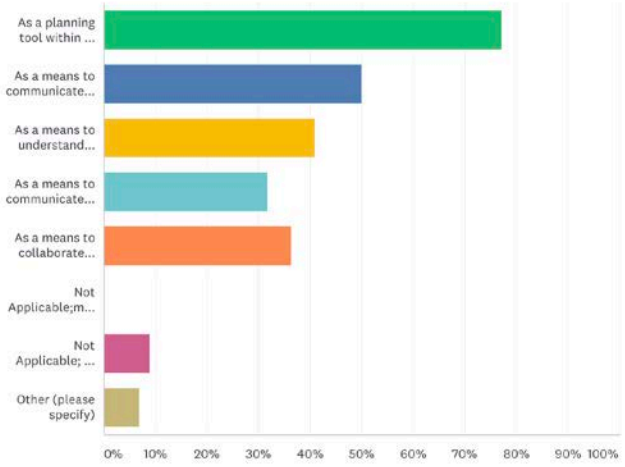
Same point as efficacy; This is my common tolerability strategy

Actual TPP Use Patterns

When I use TPPs, I start the process (select your most typical occaision)



I use Target Product Profiles in the following ways (check all that apply):



ANSWER CHOICES		RESPONSES	
As a planning tool within the project team for product development		77.27%	34
As a means to communicate product attributes to senior management		50.00%	22
As a means to understand projects proposed by those I supervise		40.91%	18
As a means to communicate with regulatory agencies about product attributes		31.82%	14
As a means to collaborate with other organizations in projects where we have a common goal		36.36%	16
Not Applicable;my company doesn't use target product profiles		0.00%	0
Not Applicable; I do not know what a target product profile is		9.09%	4
Other (please specify)	Responses	6.82%	3

Regulatory TPPs: Under- and Misused!

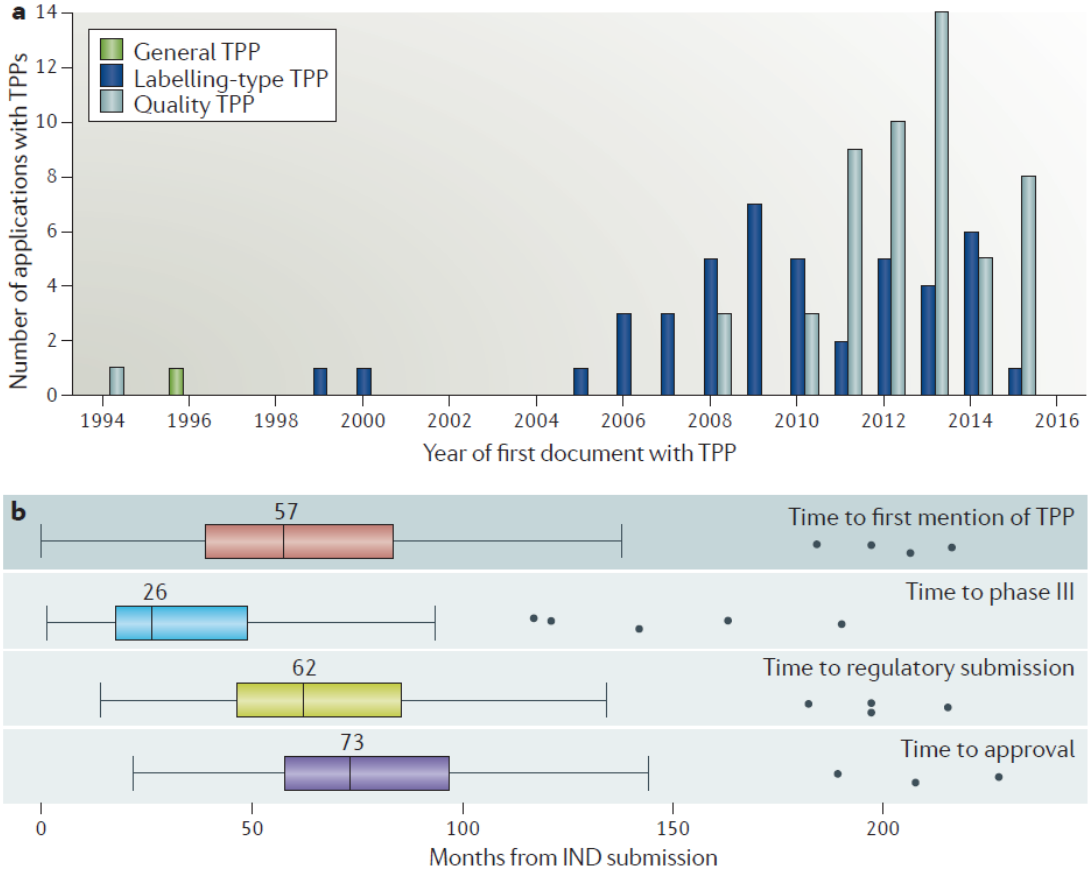
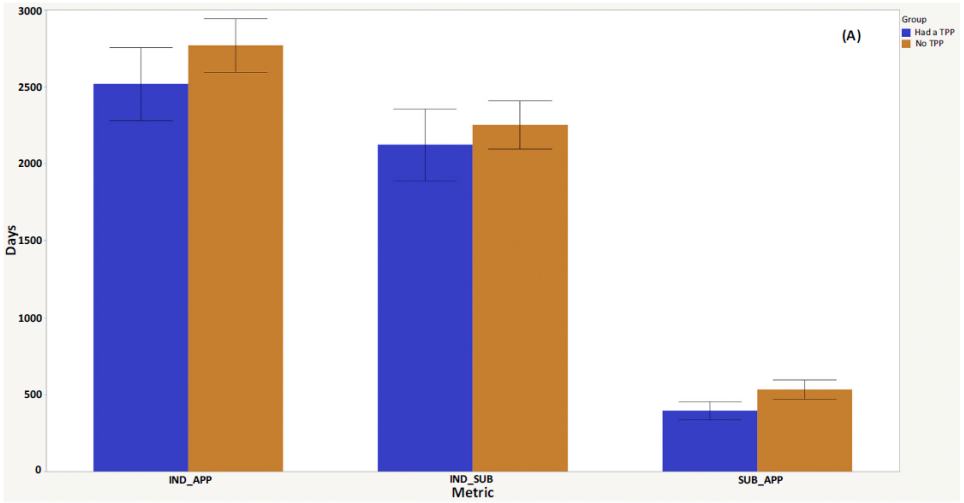
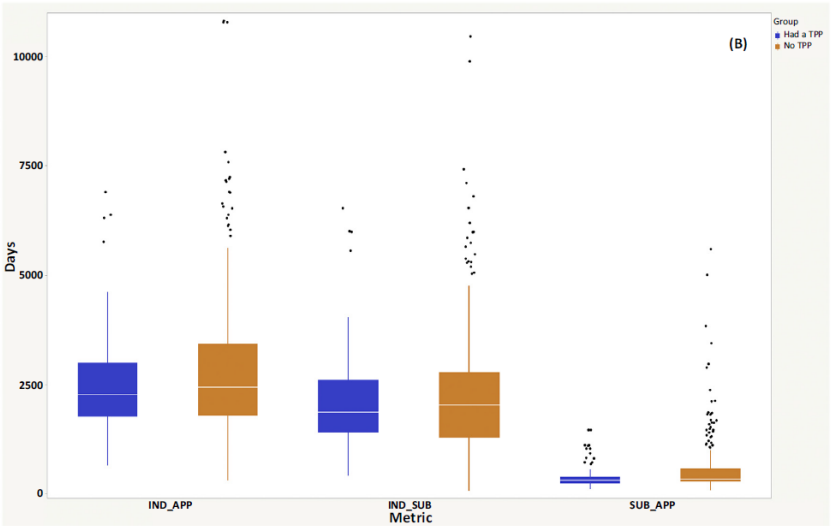


Figure 1 | **Use and impact of target product profiles. a** | Numbers of target product profiles (TPPs) per year found in regulatory documentation from the summary basis of approvals documents of drugs and biologics approved by the US FDA. **b** | Plots of median time following submission of an investigational new drug (IND) application until the first appearance of a TPP in regulatory documentation, compared with time to the first phase III study , time to submission of a new drug application (NDA) or biologics licence application (BLA), and time to approval. Boxes indicate the 25th to 75th quantile, whiskers indicate ±1.5 x the interquartile range and dots are outliers.

Benefits of 'Development by Design'

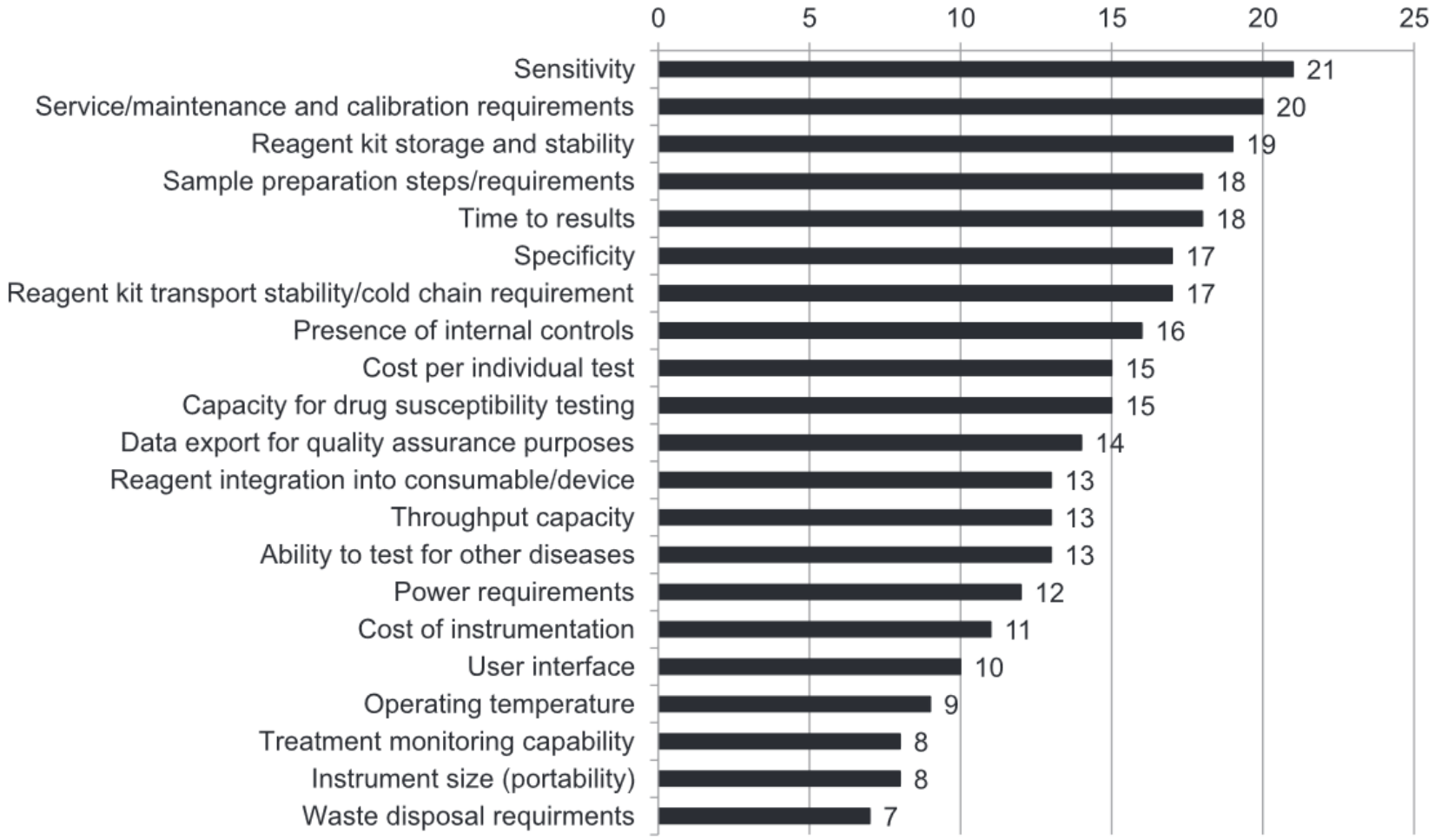




Trends in Biotechnology

Figure 2. Comparisons of Submission and Approval Metrics for New Drug and Biologic License Applications Based on Whether They Utilized Target Product Profiles. (A) Mean submission and approval metrics (error bars are 95% confidence intervals). (B) Box-and-whisker plots comparing approval metrics. The box-and-whisker plots display the median (line in box), the range of data from the 25th to the 75th quantile (box), and ± 1.5 × interquartile range (whiskers). Dots represent outliers beyond 1.5 × interquartile range. IND_APP, (B)time from Investigational New Drug (IND) application submission to approval; IND_SUB, time from IND to first marketing application submission; SUB_APP, time from first marketing application submission to approval.

Making Use of Attributes



Diagnostic test attributes ranked by survey respondents in order of importance.

INT J TUBERC LUNG DIS 22(4):425–428

http://dx.doi.org/10.5588/ijtld.17.0312

Which attributes within target product profiles for tuberculosis diagnostics are the most important to focus on?

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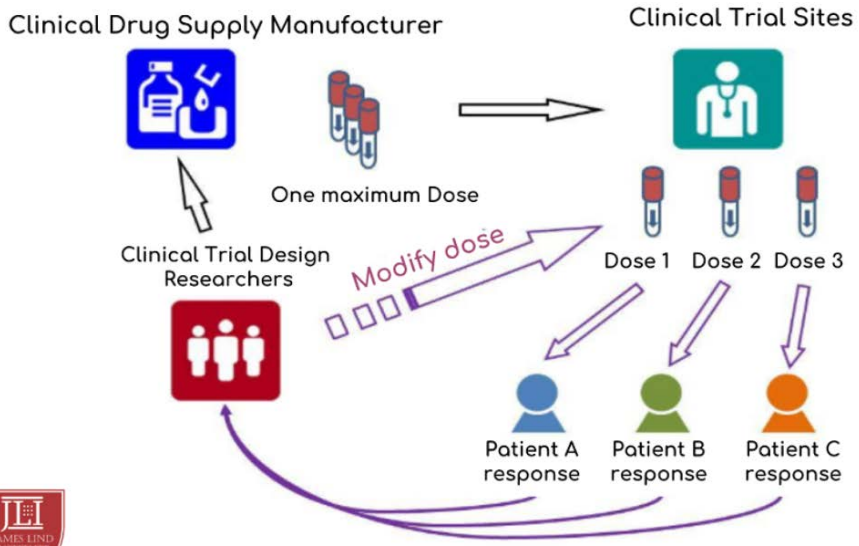
*PATH, Seattle, Washington, USA; †Burnet Institute, Melbourne, Victoria, Australia

The Present and Future of Optimizing Drug Development



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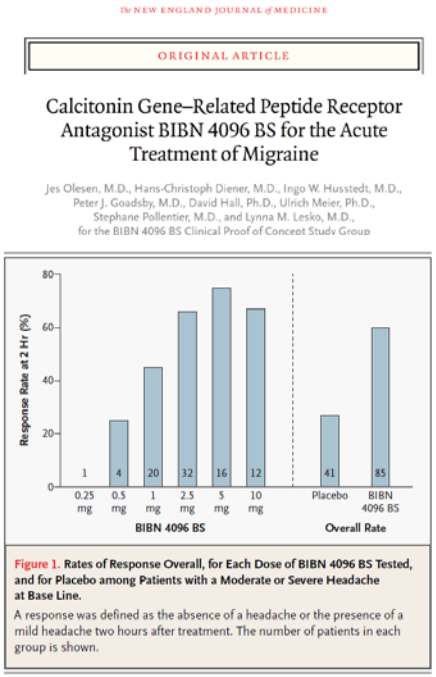

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husstedt, M.D., Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D., Stephane Pollentier, M.D., and Lynna M. Lesko, M.D., for the BIBN 4096 BS Clinical Proof of Concept Study Group

Figure 1. Rates of Response Overall, for Each Dose of BIBN 4096 BS Tested, and for Placebo among Patients with a Moderate or Severe Headache at Base Line.

A response was defined as the absence of a headache or the presence of a mild headache two hours after treatment. The number of patients in each group is shown.

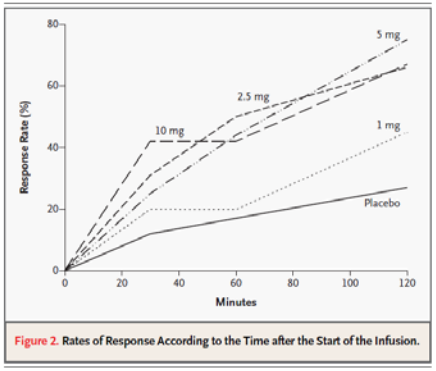

Figure 2. Rates of Response According to the Time after the Start of the Infusion.

…next generation, utility functions containing BOTH efficacy and safety?

Optimizations are Possible in Development

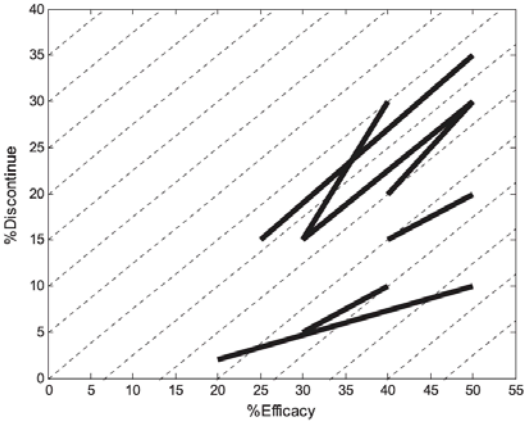

Figure 2. Trade-off between the efficacy and discontinue combinations as elicited from the clinical team (each solid line represents a pair). The efficacy and tolerability tradeoff was determined by taking the average of ratio of change in discontinue (tolerability) and change in efficacy across scenarios. This resulted in 0.7595 so we decided on 0.75 (4 points efficacy=3 points discontinue).

PLOS ONE

RESEARCH ARTICLE

Optimizing Trial Designs for Targeted Therapies

Thomas Ondra[1*], Sebastian Jobjörnsson[2*], Robert A. Beckman[3,4], Carl-Fredrik Burman[2,5], Franz König[1], Nigel Stallard[6], Martin Posch[1*]

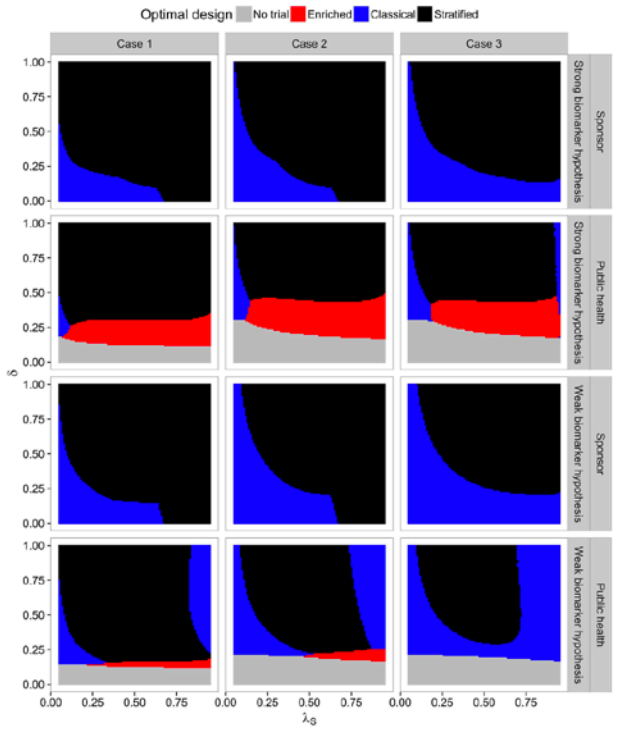

Fig 4. Optimal designs for different combinations of the prevalence $\lambda_S \in [0.05, 0.95]$ and effect size parameter $\delta \in [0, 1]$. Optimized designs for the sponsor and the public health authority are shown for both the weak and the strong biomarker prior (as defined in Table 1) under the three different cost structures defined by Cases 1, 2 and 3. The colour in a specific point indicates the type of the optimal design. Grey areas correspond to regions where all optimized designs have negative utilities, implying that the optimal choice is to perform no trial.

doi:10.1371/journal.pone.0163726.g004

Statistics in Medicine

Research Article

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Utility-based optimization of phase II/III programs

Marietta Kirchner,[a*†] Meinhard Kieser,[a] Heiko Götte[b] and Armin Schüler[b]

Why Johnny Can't 'Adapt'

Text from recent publication on optimizing trial design

$$E[c(n_2,\kappa)] = \left(c_{02} + c_2 \cdot n_2/\pi_2\right) + \left(c_{03} \cdot \int\int_{-\infty}^{\infty} 1_{\hat{\theta}_2 \geqslant \kappa} \cdot f\left(\hat{\theta}_2|\theta\right) \cdot f(\theta)\, d\hat{\theta}_2\, d\theta + c_3/\pi_3 \cdot \int\int_{-\infty}^{\infty} n_3 \cdot 1_{\hat{\theta}_2 \geqslant \kappa} \cdot f\left(\hat{\theta}_2|\theta\right) \cdot f(\theta)\, d\hat{\theta}_2\, d\theta\right)$$

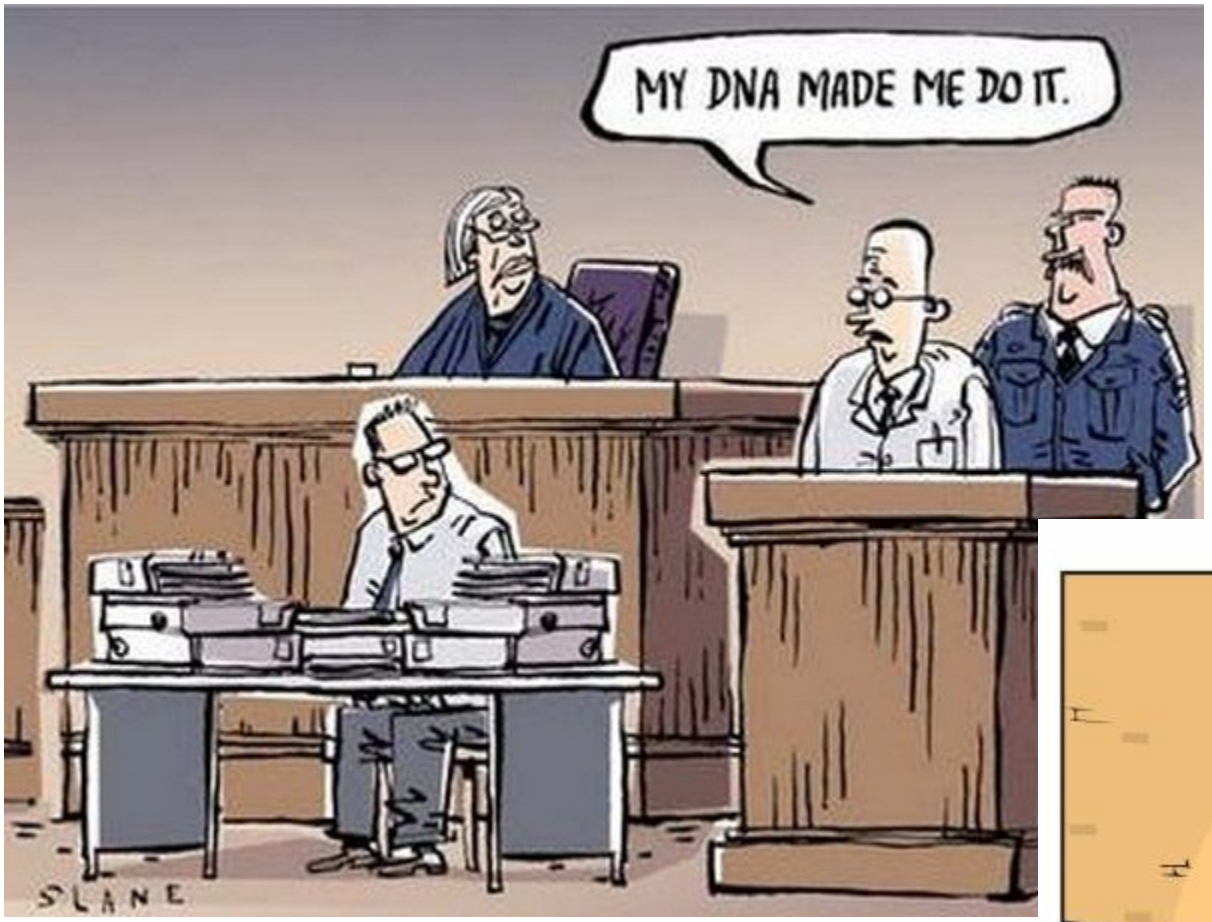
$$= \left(c_{02} + c_2 \cdot n_2/\pi_2\right) + \left(c_{03} \cdot \int\int_{\kappa}^{\infty} f\left(\hat{\theta}_2|\theta\right) \cdot f(\theta)\, d\hat{\theta}_2\, d\theta + c_3/\pi_3 \cdot \int\int_{\kappa}^{\infty} n_3 \cdot f\left(\hat{\theta}_2|\theta\right) \cdot f(\theta)\, d\hat{\theta}_2\, d\theta\right)$$

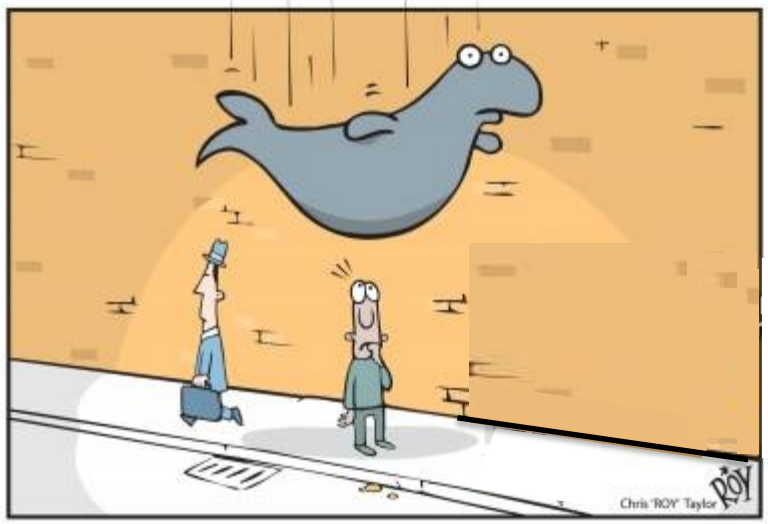
$$E[g(n_2,\kappa)] = \sum_{j=1}^{3} b_j \cdot \int\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} 1_{T_3 \in I_j} \cdot f\left(t_3|\theta,\hat{\theta}_2\right) \cdot f\left(\hat{\theta}_2|\theta\right) \cdot f(\theta)\, d\hat{\theta}_2\, dt_3\, d\theta$$

$$= \sum_{j=1}^{3} b_j \cdot \int\int_{I_j}\int_{\kappa}^{\infty} f\left(t_3|\theta,\hat{\theta}_2\right) \cdot f\left(\hat{\theta}_2|\theta\right) \cdot f(\theta)\, d\hat{\theta}_2\, dt_3\, d\theta.$$

HOW & WHEN TO USE YOUR PLANS

Once a drug is synthesized*, its fate is sealed!

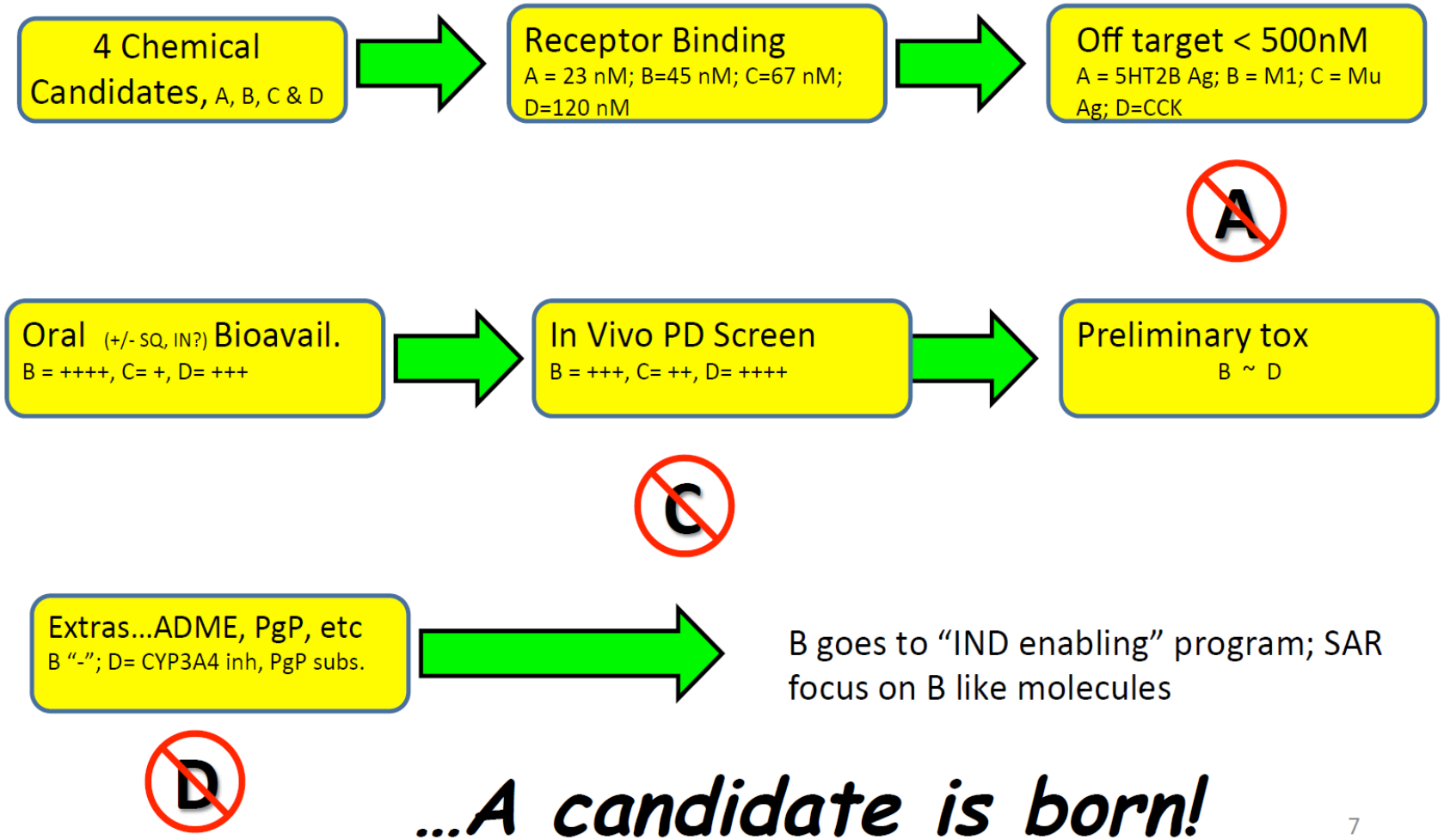




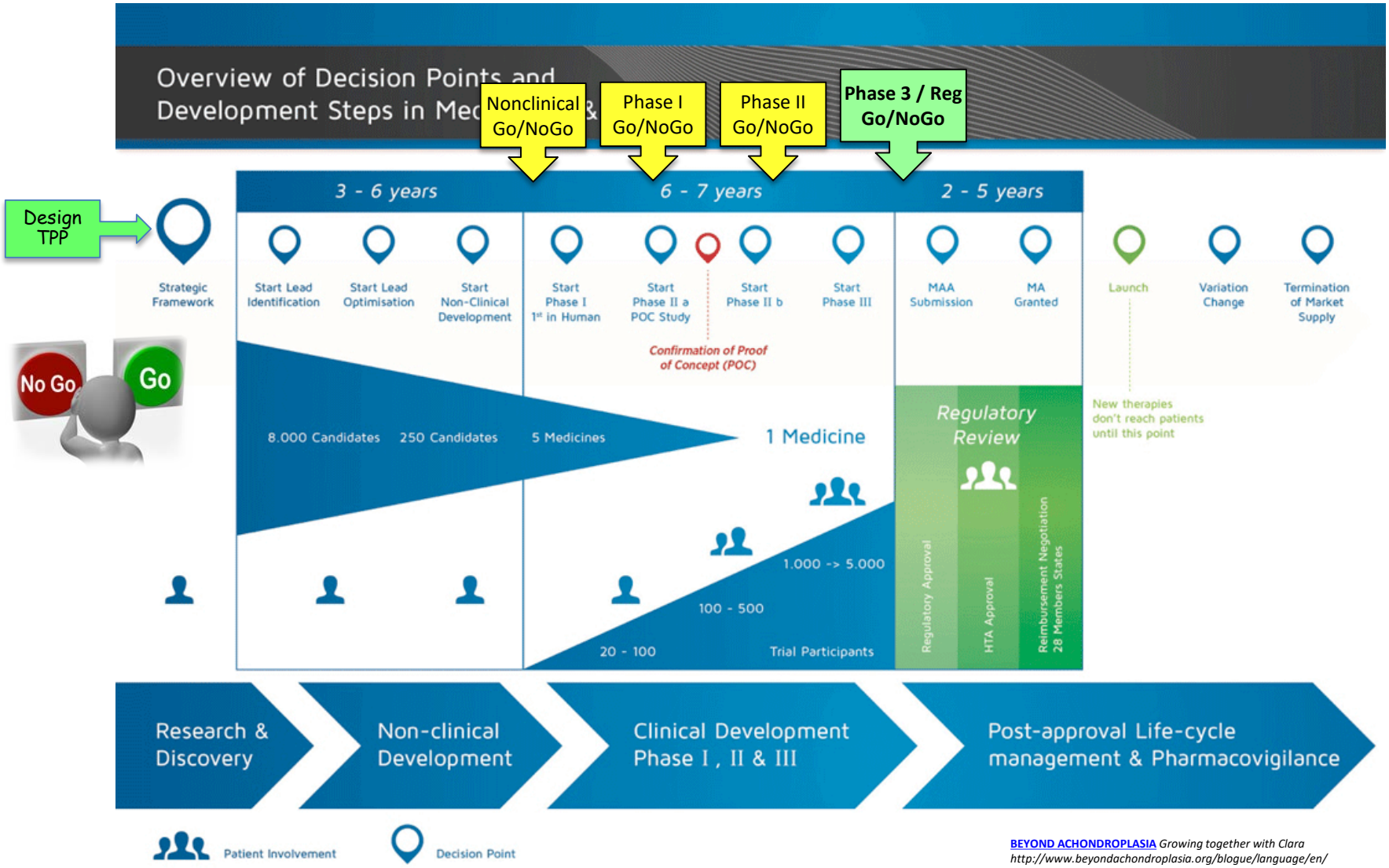
In one brief moment his fate was sealed

* + formulated

Lead Development Candidate Screening



Opportunities to Evaluate Value



BEYOND ACHONDROPLASIA *Growing together with Clara*
http://www.beyondachondroplasia.org/blogue/language/en/

Summary and Conclusions

- Proactive incorporation of optimized development features is the current standard in Quality aspects of drug development;
  - trial and program design will benefit from this methodology
- Planning and testing for trial and program design should begin before the candidate is nominated;
- Sponsors, CROs, and Regulators need to familiarize with the ‘language of planning’ and recognize the needs of other stakeholders

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