

Dose Response Assessments: Guidance, Experience, Expectations

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Disclosures and Acknowledgements

- Disclosures
 - The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.
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 - Examples - Review Teams; Publically disclosed

Outline

- I. Motivation
- II. Guidance: ICHE4, Exposure-Response, Evidence of Effectiveness
- III. Examples
 - a. EOP2A - Pain
 - b. Depression
- IV. Regulatory Expectations

Why invest in Dose Response?

- Conducting confirmatory phase III trials is expensive
- Identifying “right” dose is and should be the key goal of every clinical development program:
 - too high a dose can result in unacceptable toxicity
 - too low a dose decreases chance of showing efficacy
- **Two main goals in early development:**
 - **proof-of-concept (PoC) – any evidence of treatment effect**
 - **dose-selection – which dose(s) to take into phase III?**
 - **minimum effective dose (MED), maximum safe dose (MSD)**
by pairwise comparison of doses or. Documenting change in slope with changes in concentration
- Develop a framework for regulatory decisions and dose optimization

Recent Advisory Committee Meeting (1 of 4)

Metabolic and Endocrine

Parathyroid Hormone (Ind. Hypoparathyroidism) – Sep, 2014

Review - A system pharmacology approach applied to recommend an alternate dosing regimen

“..described their votes as “on the fence”, ...general belief that the company conducted its pharmacokinetic/pharmacodynamic study too late in the game leading to less than adequate dosing being brought forward in Phase III and for approval” – Pink Sheet, September 16 2014

FDA Reviewers Dose Response Assessment in:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugs/AdvisoryCommittee/ucm386727.htm>

Four recent Advisory Committee Meeting (2 of 4)

Dermatology

Secukinumab (Ind. Psoriasis) – October, 2014

Review - Exposure Response analysis suggested a need for a higher dose in subjects with higher body weight

“While the panelists agreed with FDA that there was some potential to further clarify the best dose of the drug for patients of various weights, most said they didn’t want that to stand in the way of the drug being approved” – Pink Sheet, October 22, 2014

FDA Reviewers Dose Response Assessment in:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/ucm404866.htm>

Recent Advisory Committee Meeting (3 of 4)

Cardio-Renal

Edoxaban (Ind. Stroke Reduction Atrial Fibrillation) – Oct, 2014

Review - Exposure Response and need for a dose adjustment in subjects with normal renal function

“.. Cardio-renal committee votes 9-1 for approval of ..anticoagulant for stroke risk reduction in patients with nonvalvular atrial fibrillation, but only five panelists said the currently proposed 60 mg dose should be approved for patients with normal renal function given ... efficacy results in this subpopulation.” – Pink Sheet, November 2, 2014

FDA Reviewers Dose Response Assessment in:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm378911.htm>

Recent Advisory Committee Meetings(4 of 4)

Oncology/Hematology

Panobinostat (Ind. Multiple Myeloma) – Nov, 2014

Review - Dose –Safety (no concentrations) assessing dose reductions relative to efficacy – overall benefit-risk assessment

“.. As a threshold issue, reviewers question whether the panobinostat 20 mg dose tested in Trial 2308 and proposed for marketing was too high of a dose. FDA’s oncology/hematology review divisions have not been shy about challenging sponsors’ dosing selection decisions in recent applications ” – Pink Sheet, November 4, 2014

FDA Reviewers Dose Response Assessment in:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm394134.htm>

Therapeutic Area – Current Trends (1 of 2)

Therapeutic Area	Phase 2	Phase 3	PMC/PMR	# of Strengths	Derived dose
Anti-Infective	2	1	rare	1	
Antiviral	3	1	rare	1	
Transplant	2	1	rare	1	
CadioRenal	3	1-2	rare	>=1	Yes
Neurology	3	2	occasional	>=1	
Psychiatry	2-3	2	occasional	>=2	Yes
Anesthesia	2	1	rare	1	
Metabolism	3	1-2	rare	1	Yes
Endocrinology	2-3	1-2	rare	>=1	
Pulmonary	3	2	rare	1	
Rheumatology	3	1-2	rare	1-2	

of strengths: Dose level approved

Therapeutic Area – Current Trends (2 of 2)

Therapeutic Area	Phase 2	Phase 3	PMC/PMR	# of Strengths	Derived dose
Dermatology	2	1-2	rare	1	
Gastroenterology	3	1-2	rare	2	
Bone	2	1	rare	1	
Reproductive	3	1-2	rare	1	
Urologic	2	1-2	rare	1	
Oncology	<=2	1	often	1	
Hematology	2	1	occasional	1	

18 Therapeutic Divisions

Spectrum of:

- Acute vs. Chronic Indications
- Benefit-Risk Assessment
- Unmet medical need differs

Is uniformity feasible or should we strive towards efficient and informative trial designs and analysis approaches tailored for specific therapeutic areas ?

Optimizing Dosing of Oncology Drugs

L Minasian¹, O Rosen², D Auclair³, A Rahman⁴, R Pazdur⁴ and RL Schilsky⁵

The purpose of this article is to acknowledge the challenges in optimizing the dosing of oncology drugs and to propose potential approaches to address these challenges in order to optimize effectiveness, minimize toxicity, and promote adherence in patients. These approaches could provide better opportunities to understand the sources of variability in drug exposure and clinical outcomes during the development and premarketing evaluation of investigational new drugs.

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Guidance on Dose Response

ICH E4 [Dose-Response Information to Support Drug Registration, 1994] links dose response to safe and effective use of drugs

FDA 2004 [Exposure Response Analysis] speaks to linking concentration and response

Other Guidance also refer to assessment of DR

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products - 1998

ICH-E4: Dose Response (DR)

ICH E-4 - first guideline largely focuses on the randomized, parallel, principally placebo controlled studies

Regulations call for integrated summaries of safety and effectiveness that provide evidence to support the dosing regimen and dose adjustments in specific subsets

Strongly encourages assessment of DR in every stage of development and to know shape and location of DR for favorable and unfavorable effects

Identified randomized, parallel, fixed dose, dose-response study, generally with a placebo group (the dose can be titrated to the fixed dose) as the gold standard,

Other trial designs include:

- Crossover designs
- Forced titration designs

ICH-E4: Dose Response (DR)

What to do with DR data has been less prescribed, recognizing that practices differ and a good deal of judgment is involved.

Two issues:

1. Interpreting the D/R curve
 2. Choosing the starting dose
-
- Almost always deficient with respect to individual D/R relationships
 - Number of doses to be included
 - Model averaging approach vs best model approach
 - Assessment of safety for dose selection:
 - Usually model is built for efficacy but not for safety
 - Hard to assess long term safety in tolerability/ dose ranging studies
 - Dose reduction/ discontinuation rules

Exposure Response Guidance

Covers:

(1) importance of integrating E-R relationship assessment in all phases of drug development

(2) points to consider while designing an E-R study and,

(3) format and content of reports of E-R studies

- The selection of appropriate exposure metric (C_{max} , AUC, C_{min})
- Caveats of over estimation of steepness of C-R relationship when disease severity is confounded with efficacy, especially for biologics
- Survival model vs logistic regression: the consideration of time as a variable

Challenges

1. Optimal dose not a requirement by law
 2. Development cost, cycle times (benefit of “learning” phase)
 3. No overall consensus on risk/benefit balance which is disease specific and balanced by availability of other treatments
- Can conduct adequate dose response studies however, dose selection “criteria” can vary which is the larger issue

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RESEARCH LETTER

US Food and Drug Administration and Design of Drug Approval Studies

To enhance protocol quality, federal regulations encourage but do not require meetings between pharmaceutical companies and the US Food and Drug Administration (FDA) during the design phase of pivotal studies assessing drug efficacy and safety for the proposed indication.¹ These meetings often generate FDA recommendations for improving research, although companies are not bound to follow them.

Companies can also request special protocol assess...

Table 1. Details of New Drugs Approved Between February 1, 2011, and February 29, 2012, and Contact Between the FDA and Pharmaceutical Companies During the Pivotal Study Design Phase^a

	New Drug Approvals (n = 35) ^b
Review history of new drugs	
Approved at the first review	24 (69)
Advisory committee meeting held	18 (51)
Study characteristics, median (range)	
No. of studies	2 (1-6)
No. of people in largest study	666 (27-18 758)
Longest study in application, mo	11 (<1-36)

Yet companies are not required to meet with the FDA or follow their recommendations. One-quarter of approvals occurred without any meeting, and when such meetings occurred, companies did not comply with one-quarter of recommendations. The FDA endorsed SPAs for only 12 of the 35 approvals, suggesting missed opportunities for optimizing study quality.

EOP2A Example – Tapentadol, Questions ?

- Does FDA concur with our choice of 46 mg as the minimum target dose for Phase 3?
- Does FDA concur with our choice of 93 mg as the maximum target dose for Phase 3?
- Does the FDA concur that a study design with fixed doses within a specified time interval (every 4 to 6 hours) will be acceptable and support labeling for a “q. 4 to 6” hour dosing interval ?
- Labeling instructions and interpolation of doses

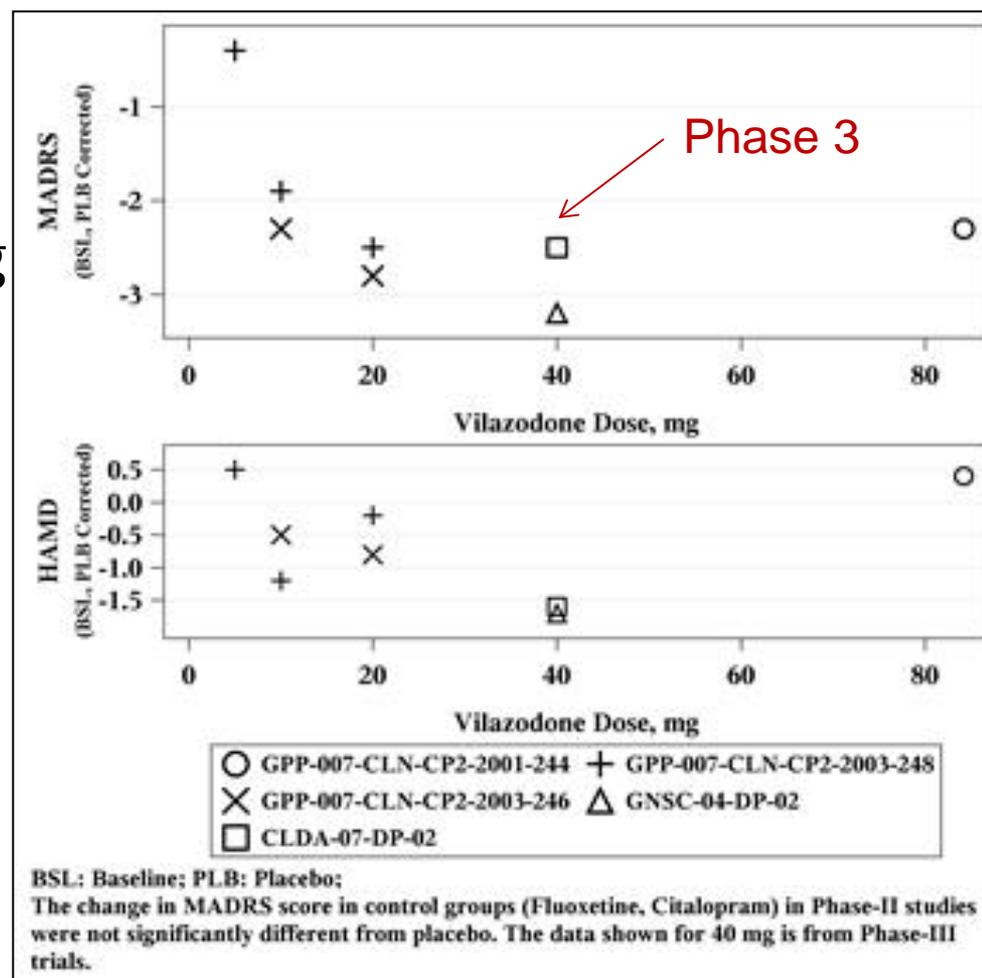
The Learning in EOP2A was Applied and Confirmed in Registration Trials

- 1, Population PK Analysis
2. Concentration – Pain Model
3. Rescue Medication for Pain Relief
4. Dose Safety

Initiate NUCYNTA[®] with or without food at a dose of 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon pain intensity. On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended. (2)

Example: Vilazodone

- Ind. Depression
- HAMD and GI tolerability
- Phase 2 studies up to 90 mg
- 40 mg initially approved,
- F/up PMR with **20 mg**



Summary

- Expect good rationale to support dose selection for phase 3 trials
 - Dose finding phase 2 (early) trials to cover full dose-response range
- More therapeutic area target the minimum dose with near maximum efficacy – move towards rational dose selection (esp. pulmonary, rheumatology, and oncology)
- Strive towards efficient and informative trial designs and analysis approaches tailored for specific therapeutic areas
- Dose optimization often after phase 3 trials (Session 5)
 - PMR
 - PMC



Thank you!