Critical Thinking & Decision-Making

Case Studies of Vandetanib and CMC Process Changes

APEC Advanced GRevP Workshop

FDA Alumni Association International Network
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FDA Alumni Association International Network

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Disclaimer of FDAAA Members

- We ARE currently employees of pharmaceutical companies, namely Celgene, Abbott, Merck and Pfizer pharmaceutical respectively. The expenses for Dr. Houn, Li and Goldbergers' travel are being paid by our employers. We thank Taiwan FDA for sponsoring Dr. Chen.
- We worked at the U.S. Food and Drug Administration (FDA) in various capacities in the past;
- We are members of FDA Alumni Association (FDAAA). The following are our views and not necessarily the views of FDAAA or FDA.

Source Data - All Public Information

All information used in these case studies come from……..

- Approval Package (FDA Website) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022405Orig1s000TOC.cfm
- Oncologic Drugs Advisory Committee (FDA Website) http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm236807.htm
- CMC applications and guidances (FDA Website) http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm

- Understand the foundation and application of critical thinking and decision-making principles

- Understand key concepts in regulatory decision making related to
  - Unmet medical need
  - Efficacy and Safety assessment
  - Risk management, including dose selection

- Understand issues with CMC process changes from Phase 3 to application submission

Educational Objectives

An Active and Group Learning Process

Approach

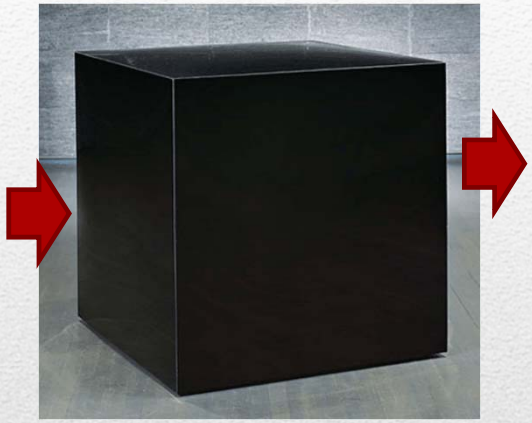
Agenda

Time	Topics	Slide #
09:00-09:30	Fundamentals in Critical Thinking & Regulatory Decision-Making	8-14
09:30-10:45	Application of Critical Thinking in Regulatory Decision-Making: Clinical • Unmet Medical Needs • Efficacy and Safety • Risk Management, including dose selection	 16-19 20-29 28-35
10:45-11:30	Application of Critical Thinking in Regulatory Decision-Making: CMC	36-45
11:30-12:00	Summary (Combined Sessions)	

Fundamentals in Critical Thinking & Regulatory Decision-Making

Session I: 9:00-9:30

Regulatory Decision-Making



In your agency,

- Who makes the approval decisions? Who recommends approval?
- How are disagreements handled?
- Is the public or patients involved in decision making? Would this be helpful or not?

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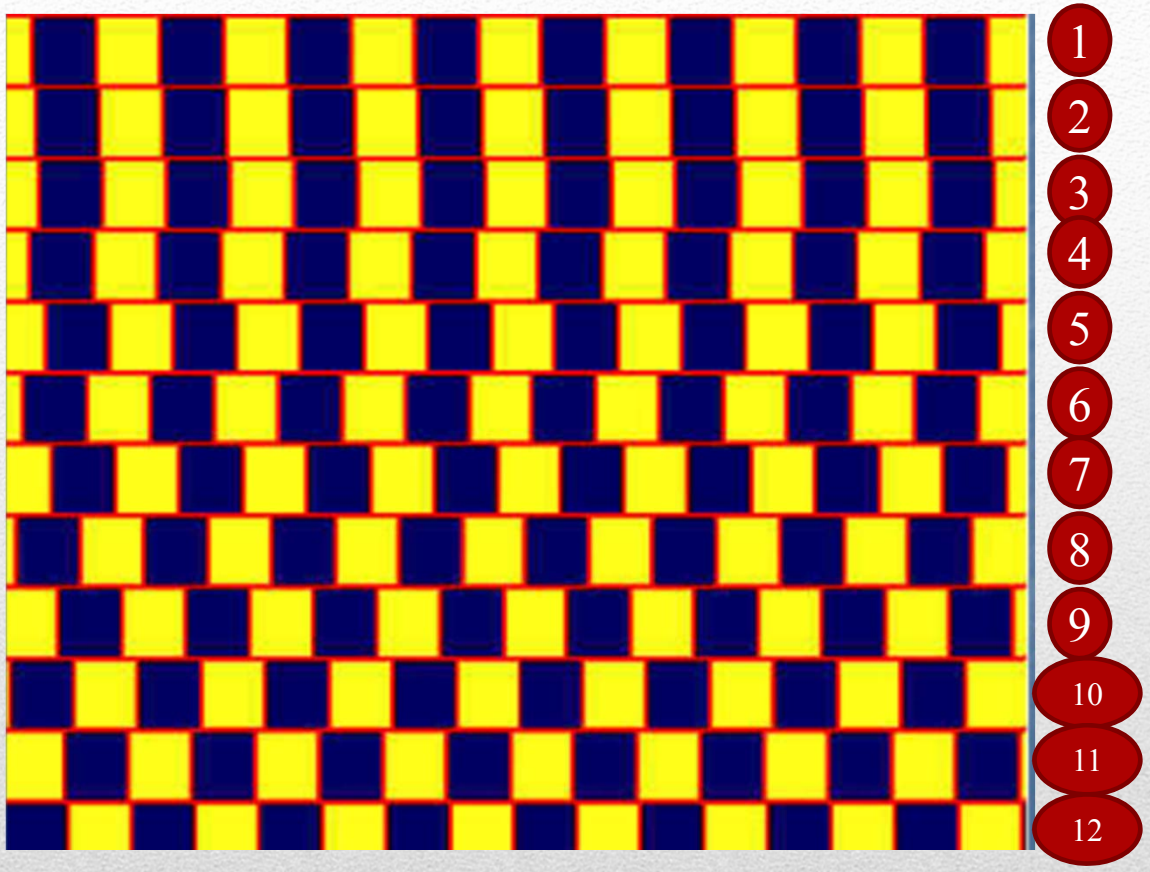
- Left = Right
- Left > Right
- Left < Right



Question #1

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What do you see here ?

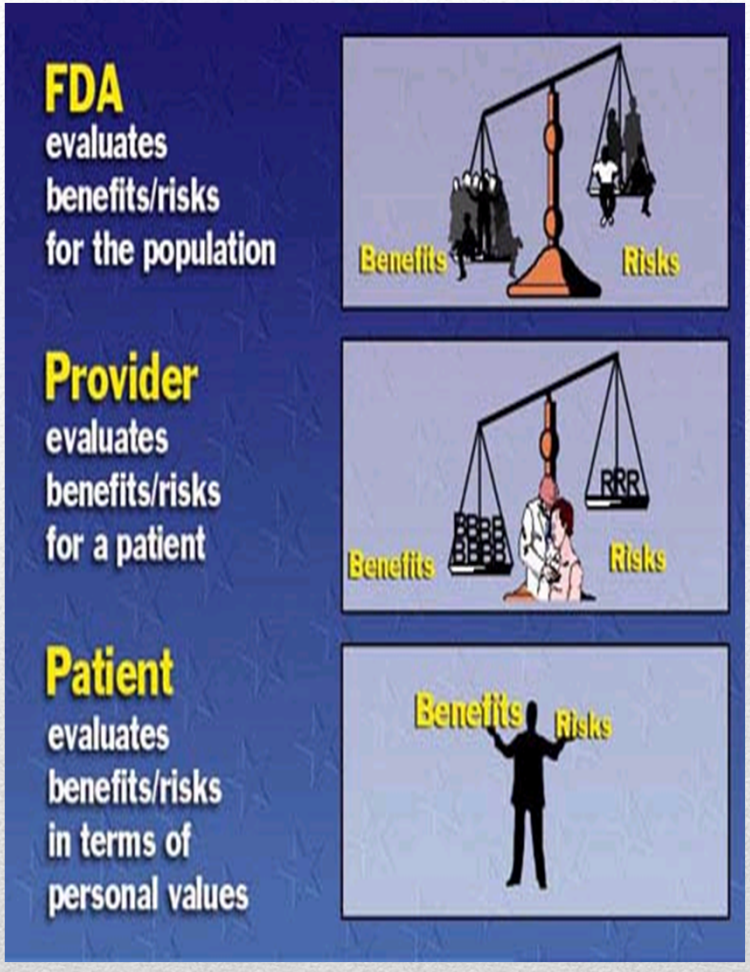
Question #2

- **Critical Thinking** is a set of skills, abilities, and dispositions to analyze evidence, apply reasoning, and form creative processes that show mastery of content and allow advancement of the discipline's mental center.
- **Regulatory Thinking** is the mastering of key legal, policy, scientific, medical, and public health principles that are incorporated into a judgment to make sound regulatory decisions
  - "Thinking like a regulator" is high performance.

Critical Thinking, Regulatory Thinking & Science-Based Regulatory Decision-Making

- Systematic approach to assessment of data
  - Thorough and without bias
    - Review Templates, Standard Operating Procedures
  - Risk-based approaches given limits of resources
- Fact (Data)-based
  - Meet legal standard for a regulatory decision
- Logical decision-making techniques
  - Transparent, predictable , free from undue influences
- Judgment: What is best for public health?

Critical Thinking, Regulatory Thinking & Science-Based Regulatory Decision-Making



Issue #1: Population vs. Individual

- If a drug is not effective in a population taking the drug, those patients experience risk without benefit
- If a drug is not effective in a patient taking the drug (.i.e. non-responder, that patient experiences risk without benefit

Issue #2: Absolute vs. Relative

- Risk vs. Benefit
- Risk/Benefit vs. Risk/Benefit

Risk/Benefit Assessment

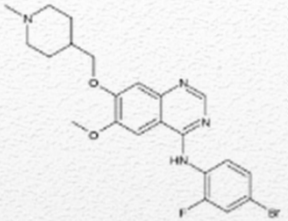
Application of Critical Thinking in Regulatory Decision-Making: Clinical

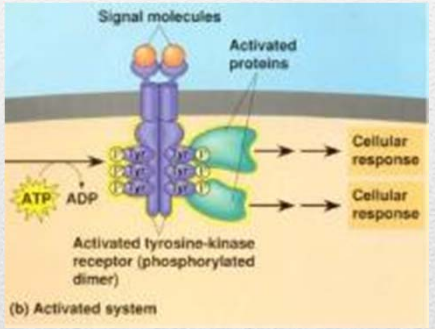
- Unmet Medical Needs
- Efficacy and Safety
- Risk Management, including dose selection

Session II: 9:30-10:45

Here is how the story started……

- The company discovered a new chemical entity
- It is a kinase inhibitor of a number of cell receptors, mainly the vascular endothelial growth factor receptor (VEGFR), the epidermal growth factor receptor (EGFR), and the RET-tyrosine kinase
  - Inhibition of tumor angiogenesis, tumor growth, vessel permeability, and metastasis
- 300mg oral tablet once daily; half-life: 19 days
- Interested in treating Medullary Thyroid Cancer (MTC)

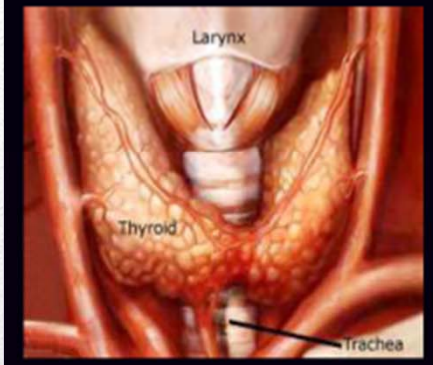




Vandetanib

Structure, Mechanism and Disease of Interest

Thyroid Anatomy and Physiology

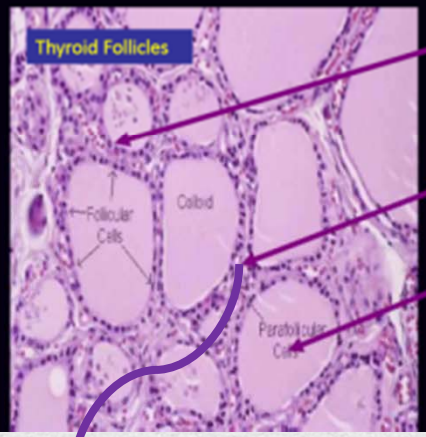


Thyroid function:

- Thyroid critical for brain and somatic development
- Affects nearly all organs
- Regulates metabolism
- Calcium and phosphorus homeostasis

Anna Gramza MD, NIH/NCI Nursing Grand Rounds Nov. 2, 2011
http://clinicalcenter.nih.gov/nursing/events/slides/Thyroid_Cancer_1.pdf

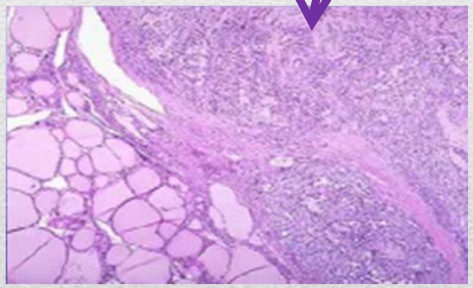
Thyroid Histology



Follicular Cells: stimulated by TSH to convert thyroglobulin to T4

Parafollicular (C) cells: synthesize calcitonin

Colloid: storage material for thyroglobulin

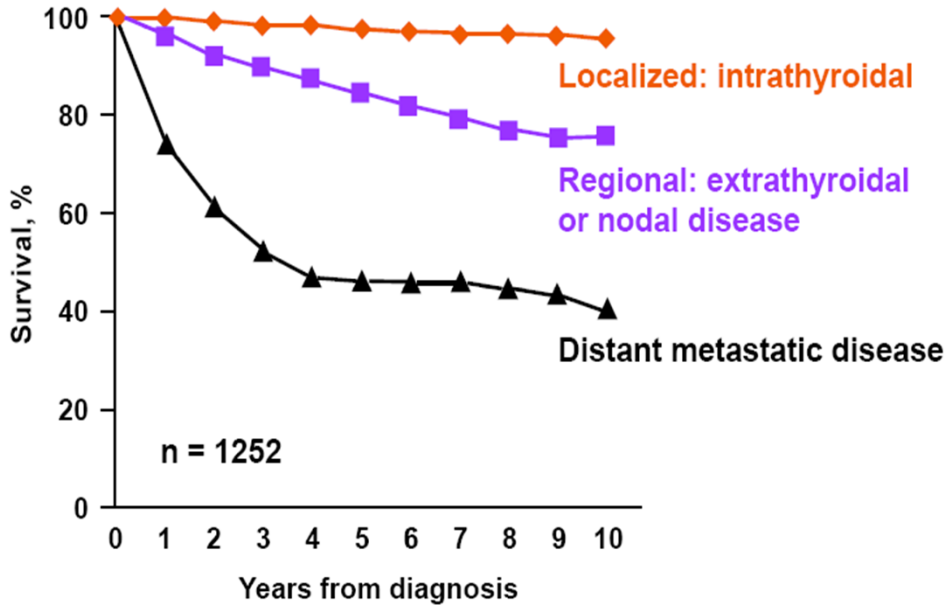


Understanding Medullary Thyroid Cancer

- 2000 patients diagnosed in US/year
- Most with localized disease; 15% Distant Metastatic disease
- No approved US drugs

CD-5

Medullary Thyroid Carcinoma SEER 1973 - 2002 Disease-Specific Survival



Roman S, et al. *Cancer*. 2006;107(9):2134-2142.

Understanding Medullary Thyroid Cancer

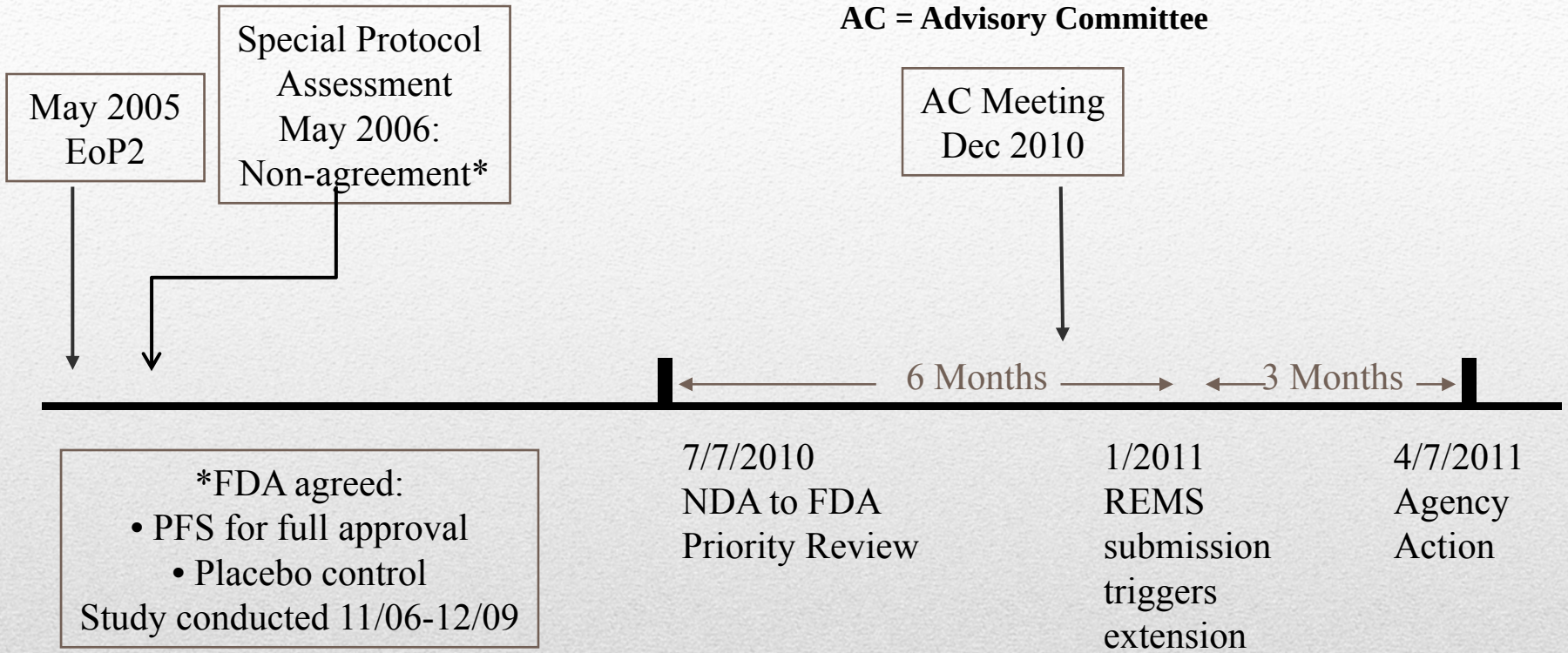
- What are your key observations from the last slide ?
- What factors do you look at to define “unmet medical need”?
- “Unmet Medical Need” is one factor in regulatory decision making. What other factors weigh in on a decision about approval?

Question

- Unmet Medical Need

Vandetanib

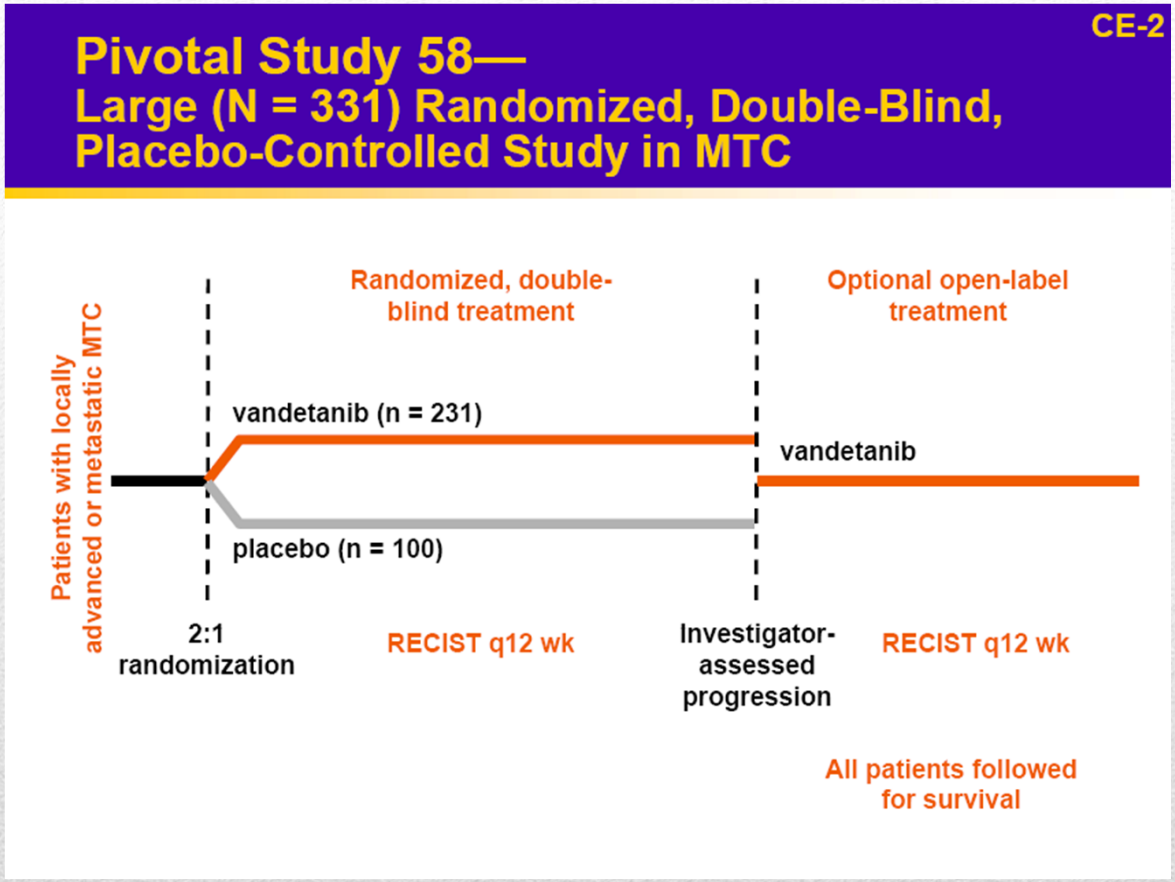
Timeline for Major Regulatory Events



Let’s go back to Dec. 2, 2010……..

Thursday December 2, 2010

FDA Advisory Committee



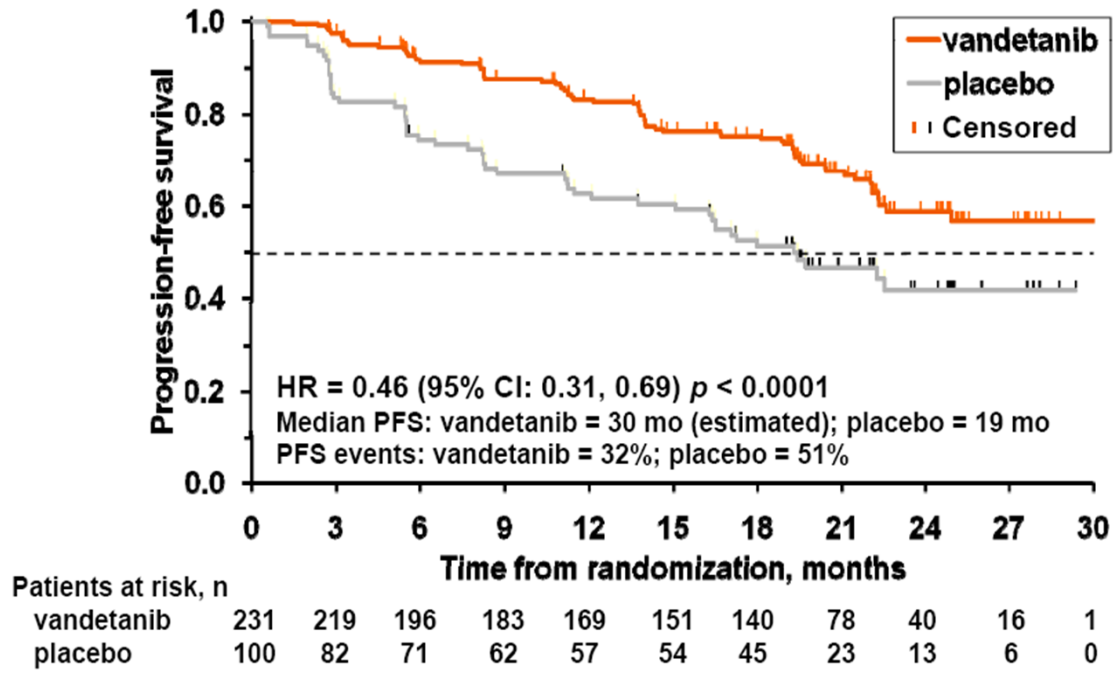
- Primary Endpoint - PFS
- Blinded Central Review
- Application of Censoring in handling missing data

Efficacy Assessment

- Phase 3 Study Design

CE-11

Early and Sustained Benefit in PFS



Please state your key observations from this slide

Efficacy Assessment

- Study Result

Based on the result presented, the company concludes, "Significant improvement in PFS…sustained benefit (median duration of PFS has not been reached)."

- Are there any other data you would like to see that could help better understand the clinical benefit of vandetanib ?
- Discuss what is statistical significance vs. clinical significance for you in this case for PFS?

Question

CE-7

Baseline Disease Characteristics

	Patients, %		
	vandetanib n = 231	placebo n = 100	Total N = 331
Hereditary MTC	12%	5%	10%
Sporadic MTC	88%	95%	90%
Locally advanced disease	6%	3%	5%
Metastatic disease	94%	97%	95%
Local disease or 1 metastatic site	13%	8%	11%
≥ 2 Metastatic sites	87%	92%	89%
No prior systemic therapy	61%	58%	60%
≥ 1 Prior systemic therapy	39%	42%	40%

CE-12

Predefined PFS Sensitivity Analyses

	HR (95% CI)	*p* value
Primary analysis	0.46 (0.31, 0.69)	0.0001
	ITT based	
Cox model with covariates	0.46 (0.32, 0.68)	0.0001
Per protocol	0.45 (0.30, 0.68)	0.0002
Timing of assessments	0.51 (0.35, 0.72)	0.0002
RECIST modification: Calcified lesions	0.47 (0.31, 0.70)	0.0002
RECIST modification: Hypodense/intense lesions	0.49 (0.33, 0.72)	0.0003
	Excluding open label	
Investigator assessments	0.40 (0.27, 0.58)	< 0.0001
Central read	0.27 (0.18, 0.41)	< 0.0001

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FDA and Applicant Primary Analyses

	FDA	Applicant
Events	30%	41%
Censored	70%	59%
Discordance	14%	0
Additional Therapy	2%	0
No Baseline Disease	10%	0
No Event	45%	59%
Hazard Ratio (95% CI)	**0.35 (0.24-0.53)**	**0.46 (0.31-0.69)**
p-value	0.0001	0.0001

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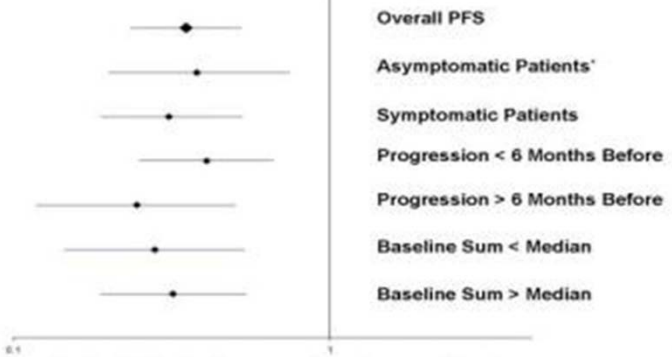
Subset Analysis



* – defined as WHO PS=0 and no pain or diarrhea at baseline

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Discussion

CS-12

QT Interval Prolongations

- Protocol criteria to define and manage QT prolongation in agreement with FDA
- Mean increase in QTcB of 25 - 30 msec generally occurs in first 30 days of dosing
- Protocol-defined QT prolongations
  - 8% (19) patients—all receiving vandetanib
  - 2 patients discontinued vandetanib for QT prolongation
  - No Torsade de Pointes (TdP) on Study 58
  - 2 cases of TdP in 5000 patients receiving vandetanib
    - Both patients recovered after discontinuation of vandetanib
- Risk management

QT Safety - Sponsor

QT Safety - FDA

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Safety Database: Adverse Events of Concern

Adverse Events	
Adverse Event	N = 3019
Sudden Death	11 (0.4%)
Torsade de Pointes	2 (<0.1%)
Grade 3-5 Interstitial Lung Disease	23 (0.8%)
Stevens-Johnson Syndrome	21 (0.7%)

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Clinical QTc Prolongation

"Drugs that prolong the mean QT/QTc interval by > 20 ms have a substantially increased likelihood of being proarrhythmic, and might have clinical arrhythmic events captured during drug development."

(ICH E14)

35

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Vandetanib is Proarrhythmic

- Mean increase in QTc interval was ~ 35 ms.
- >35% of patients in the vandetanib arm experienced > 60 ms increase in QTc.

Treatment	N	QTcF >500 ms	ΔQTcF >60 ms
Vandetanib	231	10 (4.3%)	82 (35.5%)
Placebo	99	0 (0%)	2 (2%)

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Drugs with Known Arrythmogenic Potential

Drug	Indication	Mean ΔQTcF, msec
Vandetanib	Medullary Thyroid Carcinoma	35
Arsenic Trioxide	Relapsed APL	47
Nilotinib	CML	18
Sotalol	Anti-arrhythmic	40
Thioridazine	Anti-psychotic	30
Propoxyphene	Pain	>25

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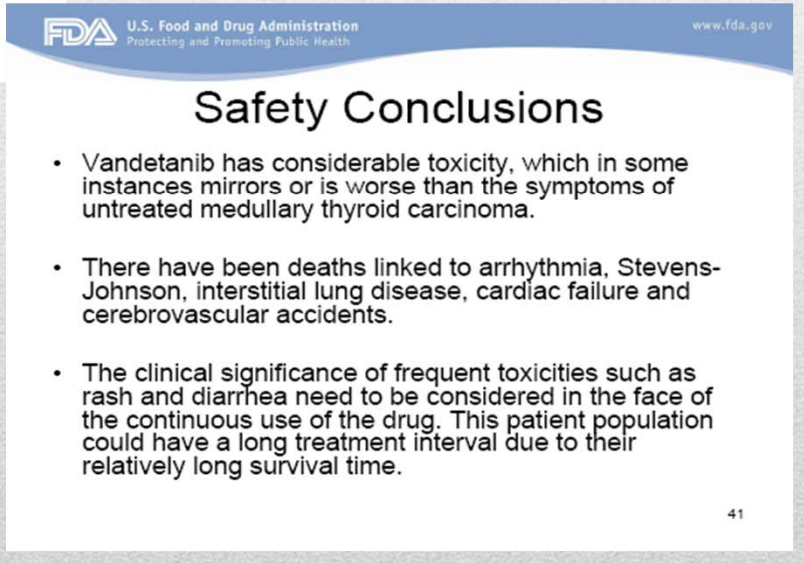
CS-16

Summary—Vandetanib Overall Safety

- All patients started at vandetanib 300 mg orally once daily
- Median duration of treatment on vandetanib = 1 year 9 months
- Dose adjusted to tolerance
  - Dose reduction to 200 mg (and 100 mg if necessary)
  - Most AEs occur in the first 12 weeks
  - 13% of patients discontinued vandetanib for an AE
- 44 patients elected to continue on vandetanib in the open-label phase



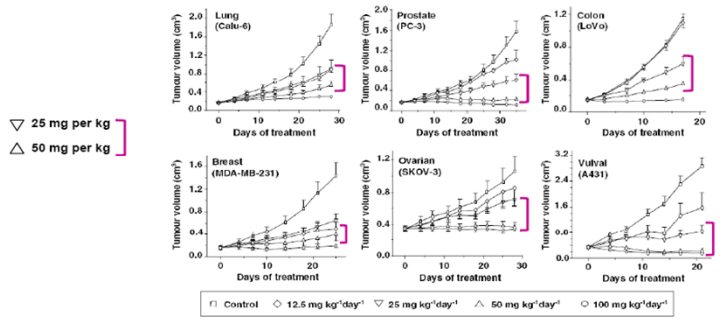
Overall Safety Assessment

- Do you agree that the FDA and the Company appear to be divergent towards overall drug safety and their interpretations of QTc and its impact ?
- In drug development, why does this arise and how can divergence be minimized ?

Questions

Rationale for MTD Dosing—Preclinical Activity of Vandetanib Over Human Dosing Range

CS-20



Ryan AJ, et al. *Br J Cancer*. 2005;92(suppl):S6-S13.

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Experience at Lower Doses

- Phase 2 studies in hereditary MTC
  - 300 mg response rate – 17% (n=30)
  - 100 mg response rate – 16% (n=19)

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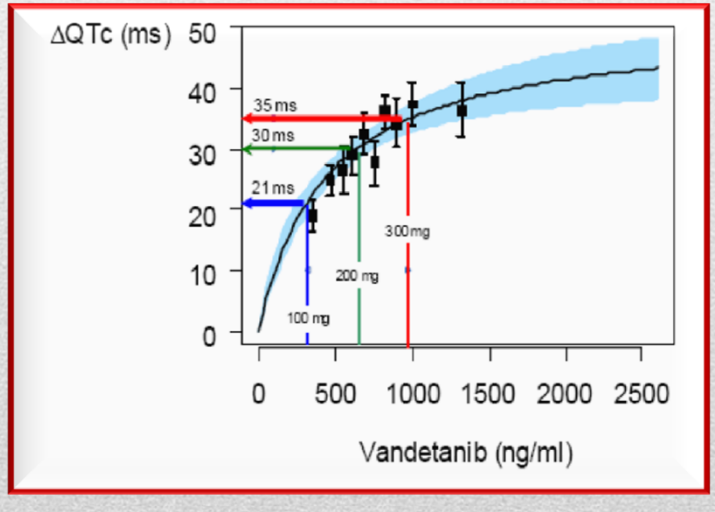

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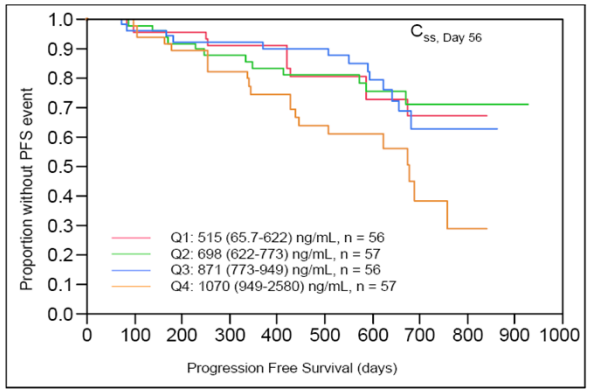
Exposure-PFS Relationship



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Revisiting Dose Selection

- Preclinical studies suggested the MTD be used. This is the usual principle for oncology dose selection and other diseases. However, Under what circumstances would a non-MTD approach be considered?
- The sponsor presented pre-clinical data to justify a higher dose. The clinical data on efficacy do not show dose/response. Q-T appears to be a dose/exposure relationship. What questions and issues come up now?

Questions

- Vandetantib was Approved by the FDA on April 6, 2011

- EMA conditional approval on Feb. 21, 2012

Drug Approvals

Oncologists usually manage serious, life threatening toxicities: cytopenias, renal toxicity, etc.

- What considerations are there for imposing risk management in oncology or any other field?
- How is success measured?
- Discuss risk management approaches

Questions

- Before the ODAC, the company proposed managing risks via labeling
- After the ODAC, a REMS with a medication guide and communication plan were proposed on Dec. 22, 2010
- On Jan. 21, 2011, FDA mandated a risk management plan be submitted that included certification of prescribers and pharmacists.
  - Prescribers must enroll with the company, read materials on risk of drug and pass a test of 6 questions.
  - Pharmacists must be enrolled and only accept prescriptions from certified prescribers.
- This is the first time FDA has required a “comprehension” test for prescriber certification. The Prescriber must be 100% correct.
- This RMP requires company resources to manage the database of prescribers and pharmacists.

Risk Management

Post-Marketing Requirements

- Clinical trial of 300mg vs. 150mg daily in MTC for safety and ORR (overall response rate)
- 2-year carcinogenicity study in mouse and rat
- Submit final OS (overall survival) analysis result in study 58 in 2014

Key Message:
- Cancer as a "Chronic Disease"

CMC Changes from IND to NDA

- A science-, risk-based approach to product and process understanding

Disclaimer: This case study is a hypothetical example developed based on the speaker's experience.

Chi-wan Chen

Session III: 10:45-11:30

* CMC = Chemistry, manufacturing, and controls

Principles on Assessing CMC Changes

- If CMC changes occur from Phase 3 to NDA, product quality and/or performance should be demonstrated to be equivalent before and after the change
- Demonstration of equivalence
  - Different levels of studies and documentation
    - Comparable results on critical quality attributes and/or specification at release
    - If necessary, comparison of additional attributes
    - Stability data, if relevant (i.e., if stability-related quality attributes are affected)
    - Comparable dissolution data/profiles
    - Relative bioavailability data, sometimes referred to as “bridging study”
    - Bioequivalence (BE) study

  - Depending on
    - Type of drug substance and product
    - Type and extent of change
    - Product and process understanding

Assessment of Effect of CMC Changes: BE Study and its Waiver

- Some major changes require bioequivalence study to demonstrate equivalence before and after the change
- Under certain situations, BE study may be waived:
  - In the presence of established in vivo/in vitro correlation (IVIVC) for modified release dosage form
  - BCS 1 with rapid dissolution for IR dosage form
- Biowaiver can be used pre-approval and post-approval

Question to the Audience

- Do you have a biowaiver policy similar to that described above?
- If yes, does it apply to pre-approval changes as well as post-approval changes?

Drug X

Drug substance

- MW 498.35, a phosphate salt
- Crystalline, single polymorphic form
- Non-hygroscopic
- BCS* Class 3 (high solubility, low permeability), though it may be considered borderline Class 1 (high solubility, high permeability)
  - Soluble in ≤ 250 ml of aqueous media over pH 1-7.5 ➡ *Meets high solubility definition*
  - 85% absorbed ➡ *Does not meet high permeability definition of ≥ 90% absorption*

Drug product

- Strength: 300 mg, once daily; total tablet weight: 600 mg
- A robust immediate release tablet dosage form containing conventional inactive ingredients and non-functional film coat
- Tablet dissolves rapidly: > 85% in 30 min at 0.1 N HCl, pH 4.5, and pH 6.8
- Undergoes predictable hydrolytic degradation with manageable stability profile

* BCS: Biopharmaceutical Classification System

Process and Other Changes

	Phase 3 batches	To-be-marketed product
Formulation	• No film coating • Magnesium stearate 0.5%	• Film coated • Magnesium stearate 1.0%
Process	Wet granulation	Dry granulation*
Scale	Pilot scale	Production scale
Site	Clinical supply site	Commercial sites A and B

* To minimize degradation due to hydrolysis during manufacturing.

Question to the Audience

- Do you consider the formulation change and/or process change major? Would you require a BE study? If yes, would you accept a biowaiver?
- Do you consider the scale-up and site transfer a major change?

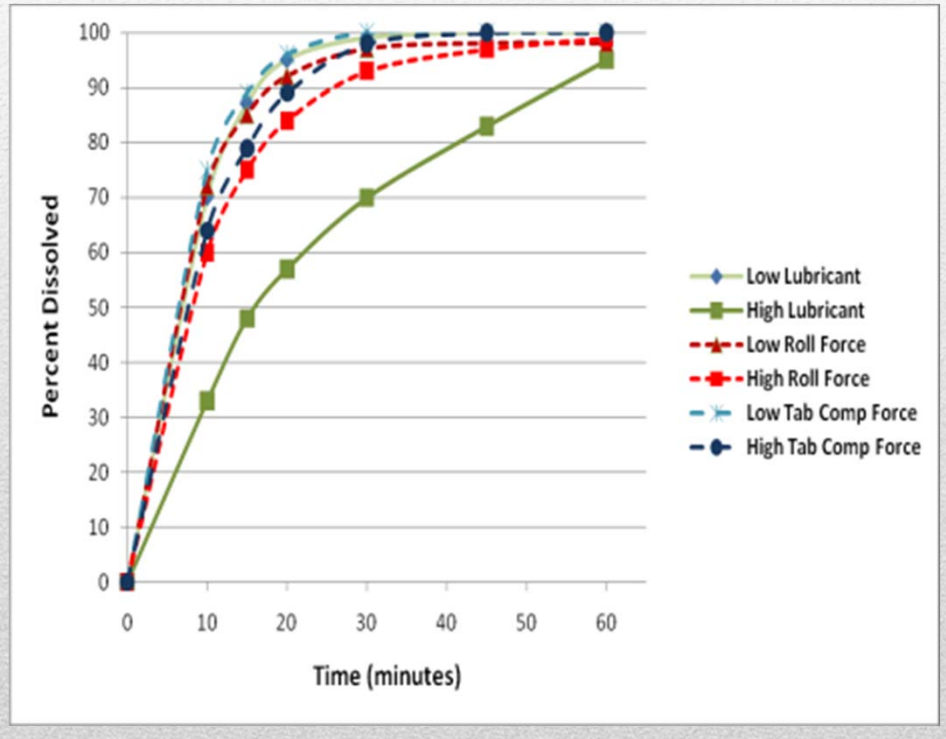
CMC Issue at a Guidance Meeting during Phase 3

- Sponsor sought agreement from the Agency on CMC changes proposal at a guidance meeting during Phase 3
  - in vitro dissolution profile comparison (in one optimal medium) in lieu of a BE study to support
    - Formulation and process changes
    - Scale-up and site transfer
  - Stability data: 3 batches/24 months from pilot site; 3 batches/6 months from commercial site A; no stability data from site B
- Agency's response
  - Recommends a BE study for the proposed formulation and process changes
  - Agrees with the BCS-3/borderline BCS-1 classification. Thus, a biowaiver may be granted if the dissolution method used can be shown to be discriminating.
  - Due to major process change, batches made at site A are considered primary stability batches. 12 months are needed at submission or in an amendment. Release data without stability data on1 batch from site B will be acceptable.

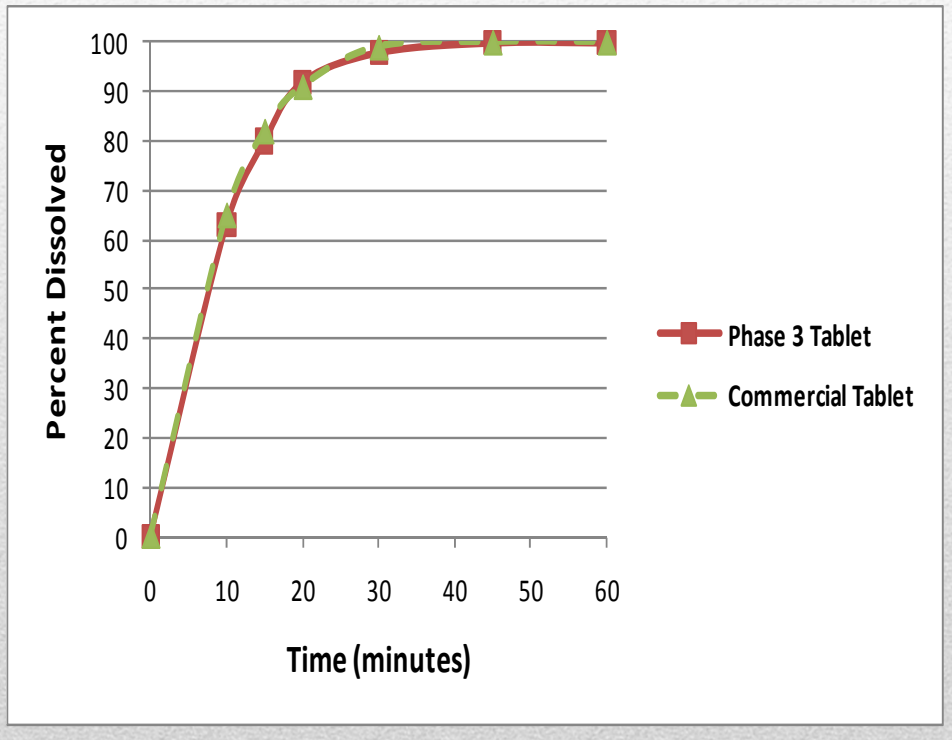
Sponsor's Data and Summary in NDA

- Product and process understanding and robustness
  - Risks of formulation/process/scale/site changes on product quality and stability understood and effects studied
  - Change to process designed to reduce degradation during manufacturing
- Equivalence of product quality
  - Comparable results of critical quality attributes at batch release and on stability before and after the changes
- Equivalence of product performance
  - Dissolution method: 0.1 N HCl, USP Apparatus II, 50 ppm
    - The method was selected as optimal based on development work with different apparatus, media/pHs, and agitation speeds
    - The method is shown to be discriminating because it is capable of detecting poor quality tablets as a result of over lubrication
    - Other process parameters, e.g., roller compaction force, tablet compression force, do not have an impact on dissolution or bioavailability

Comparative Dissolution Profiles of Drug Product X by Varying Formulation/Process Parameters



Comparative Dissolution Profiles of Phase 3 and to-be-Marketed Batches



Sponsor's Data and Summary in NDA (cont)

- Equivalence of performance demonstrated based on comparative dissolution profiles using similarity factor f_2, in lieu of BE study, between
  - a Phase 3 made with pre-change formulation and process at pilot site, and
  - a batch made with formulation and process changes at the commercial scale and site A, i.e., representative of to-be-marketed product
- Stability data and shelf life
  - Satisfactory 12 months stability data from site A, combined with 24 months data from pilot site, support the proposed 24-month shelf life
  - Comparable release data and dissolution profile in one medium from site B
  - Commitment to placing first commercial batches on stability at site B

Agency's conclusion

- Agrees with Sponsor's approaches, methods, analyses, and conclusions on these issues

Questions to the Audience

- Was the guidance meeting beneficial to the Sponsor in this case?
- What is a "discriminating" dissolution method? Is it necessary? Is it always achievable?
- Do you agree with the Agency's conclusion overall? What other data would you have requested?