

*SECOND ANNUAL WORKSHOP ON
CLINICAL OUTCOME ASSESSMENTS
IN CANCER CLINICAL TRIALS*

April 25, 2017 ■ Bethesda, MD

Co-sponsored by



Session 1
*Exploring the Concepts of
Safety and Tolerability:
Incorporating the Patient Voice*

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Session Participants

Chair

- *Bindu Kanapuru, MD* – Medical Officer, Division of Hematology Products, OHOP, FDA

Presenters

- *James (Randy) Hillard, MD* – Professor of Psychiatry, Michigan State University
- *Crystal Denlinger, MD, FACP* – Associate Professor, Department of Hematology/Oncology; Chief, Gastrointestinal Medical Oncology; Director, Survivorship Program; Deputy Director, Phase 1 Program, Fox Chase Cancer Center
- *Katherine Soltys, MD* – Acting Director, Bureau of Medical Sciences, Therapeutic Products Directorate, Health Products and Food Branch, Health Canada
- *Karen E. Arscott, DO, MSc* – Associate Professor of Medicine-Patient Advocate and Survivor, Geisinger Commonwealth School of Medicine

Panelists

- *Daniel O'Connor, MB, ChB, PhD, MFPM* – Expert Medical Assessor, MHRA
- *Eric Rubin, MD* – Vice President & Therapeutic Area Head, Merck & Co., Inc.
- *Paul G. Kluetz, MD* – Acting Associate Director of Patient Outcomes, OCE, FDA
- *Selena R. Daniels, PharmD, MS* – Team Leader, COA Staff, OND, CDER, FDA

Safety in a Changing Therapeutic Context

Prior Drug Development Era:

- Mechanism: Cytotoxic Chemotherapy
- Intermittent Intravenous Administration
- Shorter Duration of Treatment
- Relatively homogeneous adverse event profiles typically Bone Marrow Suppression, Fatigue, Hair Loss, Taste Changes



Current Drug Development Era:

- Mechanism: Diverse, including Cytotoxic, Immune, Antibodies, Small Molecule targeting Various Pathways.
- Continuous Daily Oral Administration becoming more common
- More Prolonged Duration of Treatment
- **Adverse events can differ depending on mechanism and target.**

Can lead to cumulative low grade but bothersome symptomatic toxicities

What is safety and tolerability?

ICH-E9 Statistical Principles for Clinical Trials

Section VI. Evaluation of Safety and Tolerability

“The safety of a medical product concerns the medical risk to the subject...”

The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject.”

Safety versus Tolerability

Deaths and Serious AEs might lead one to believe the treatment is reasonably safe when compared to placebo in the cancer setting, but is it tolerable?

	Treatment (%)	Placebo (%)
All Deaths	13.8	16.2
Serious AEs	44	40
Grade \geq 3 Fatigue	15	9
Grade \geq 3 Hand Foot Skin reaction	17	0
Grade \geq 3 Diarrhea	8	2

Drug related adverse events leading to permanent discontinuation: 8.2% in the treatment arm and 1.2% in the placebo group.

Dose reductions due to adverse events: 37.6% in treatment arm and 3.2% in the placebo group.

Drugs may be considered safe, but symptomatic side effects can contribute to high degrees of dose interruption or delay

Drug	Dose Interruption	Dose Reduction	Dose interruption or delay
Erlotinib	62%	19%	NA
Vandetanib	47%	49%	80%
Cabozantinib	NA	79%	86%
Ponatinib	66%	52%	74%
Ceritinib	69%	59%	71%
Idelalisib	NA	34%	53%
Lenvatinib	56%	68%	90%
Regorafenib	61%	38%	NA

Modified from Janne P, Kim G, et al. *Clin Can Res*; 22 (11); 2016

“Reviewer comment: There were several toxicities that were graded by CTC as Grade 1 and Grade 2. For instance, 2 patients discontinued due to grade 1 and grade 2 diarrhea. This highlights that even low grade toxicity is significant enough to disrupt a patient’s life and lead to discontinuation. Similarly, there were 6 patients that discontinued due to grade 1 and 2 asthenia or fatigue. Given the toxicity profile of the untreated disease state, any additional toxicity could potentially make the treatment regimen intolerable.”

Safety and Tolerability

**That's what makes
them so perfect --
they were two
different sides of the
same coin,.**

Frank Deford



U.S. FOOD & DRUG
ADMINISTRATION

The Patient Perspective

James (Randy) Hillard, MD

Professor of Psychiatry, Michigan State University



Safety vs Tolerability: A Clinician's Perspective

Crystal S. Denlinger, M.D., F.A.C.P.

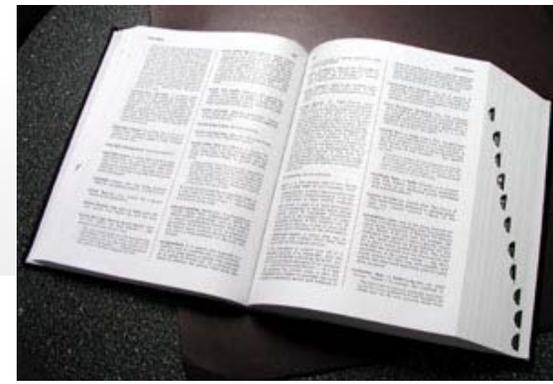
Associate Professor, Department of Hematology/Oncology

Chief, GI Medical Oncology

Fox Chase Cancer Center, Philadelphia PA



Definitions



- Safety: Risk to the patient, assessed by laboratory testing, physical exam, clinical adverse events, and other tests
 - Is this going to hurt my patient?
- Tolerability: The degree to which overt adverse events can be tolerated by the patient
 - Is this going to affect my patient's lifestyle and day to day activities?
- Effectiveness: The degree to which a drug is efficacious in treating the disease, and tolerable and adhered to by the patient.
 - Is this something my patient will take and stick with, thus giving me the chance to treat the cancer?

A Case in Drug Safety vs. Tolerability

- 53 year old woman with no other medical history
- Diagnosed with inoperable cholangiocarcinoma metastatic to liver and intra-abdominal lymph nodes in 2011
- 2011-2012: cytotoxic combination chemotherapy with initial response
 - Treatment changed (discontinuation of platinum and substitution of new cytotoxic agent) for function-limiting peripheral neuropathy
- 2013: Phase 1 trial of an oral targeted therapy
 - Remained on study for 2.5 years with sustained tumor response

A Case in Drug Safety vs. Tolerability

- Phase 1 study therapy complicated by:
 - Facial puffiness resulting in altered outward appearance
 - Lower extremity edema resulting in discomfort while standing or wearing shoes
 - Generalized swelling resulting in clothing misfit and generalized body image issues
- Ultimately off-study for progressive disease
- Treatment effects resolved after 3 months
- Enrolled in second targeted therapy study
 - Off study after 8 months due to treatment-related side effects with a tumor response

The Discussion in Clinic

- Should the drug be stopped or dose-modified?
 - Does effectiveness change with lower dose? Will drug be available in future?
- What other treatment options exist?
- Can you live with these side effects?
 - Is how you feel worth risking the benefit you are getting from the drug?
- What supportive measures can we try to make it better?

- The drug is safe, but is it tolerable for you?

A Study of Tolerability and Safety: Panitumumab

- In metastatic colorectal cancer, associated with ~10% response rate and 5 month improvement in progression-free survival
- 25% discontinue for reasons other than disease progression
- Skin-related toxicities in 90%
 - Erythema: 64%
 - Dermatitis acneiform 62%
 - Pruritis: 57%
 - Skin exfoliation: 24%
 - Paronychia: 24%
 - Skin fissures: 20%



A Study of Tolerability and Safety

- Other adverse events/side effects:
 - Fatigue 24%
 - Diarrhea 21%
 - Hypomagnesemia 36%
 - May require magnesium replacement (extra 2+ hours of infusion time)
- All manuscripts (phase 1-3 trials): “Panitumumab was well-tolerated”
 - Low number of grade 3/4 adverse events

	Grade 1	Grade 2	Grade 3	Grade 4
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-

The Discussion in Clinic

- Patient perspective: Lifestyle burden
 - Disfiguring rash
 - Itchy skin
 - Need for skin care regimen/regular sunscreen
 - Psychosocial distress regarding appearance, social or professional life
- Clinician perspective: Rash=increased chance of efficacy
 - Institute supportive care measures
 - Treatment options in this disease are limited
 - It is not *that* bad—just keep going and it will calm down
 - We know panitumumab is safe, but is it tolerable for you?



What Patients Want to Know

- Will this work for my cancer?
- What are the side effects?
- How will this affect me on a day to day basis?
- Will I be able to function normally?
 - Can I work?
 - Can I go on vacation/visit my family/see my friends?
- How will this affect my appearance?
- Can I still be around my friends and family?
- What can I expect?

- How should I plan my future while on this therapy?



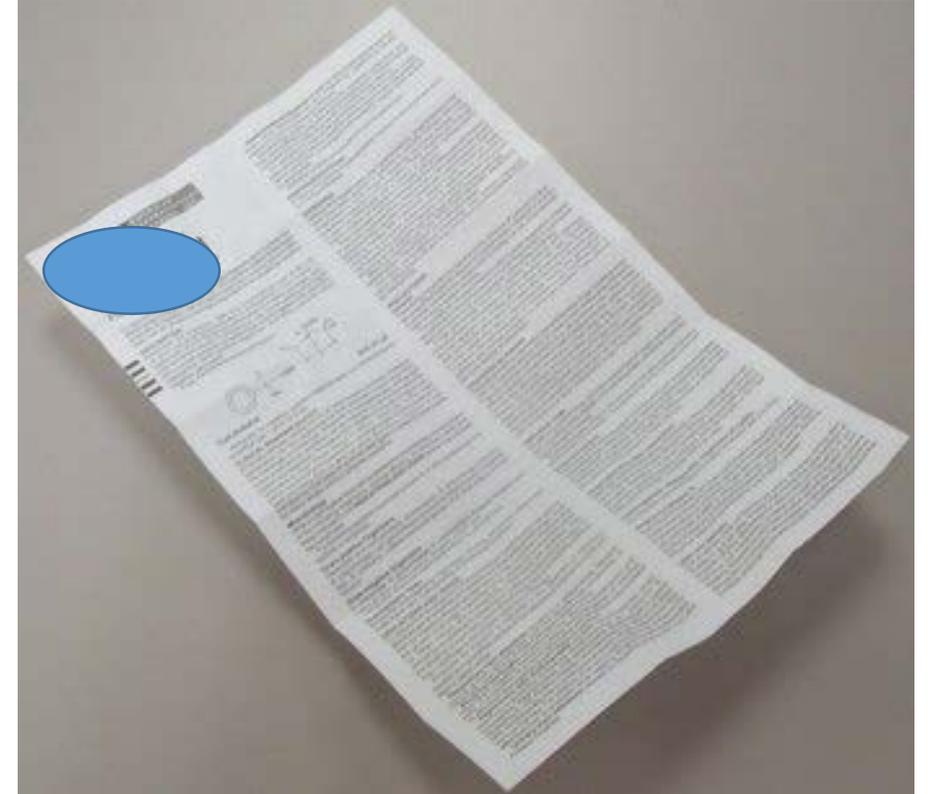
Clinician's Perspective: Discussing Therapy

- Describe common toxicities or known toxicity profile of experimental agent
- Review all the potential toxicities/adverse events
- Request report of ALL toxicities experienced, regardless of severity
- Quick review of systems as it pertains to known drug toxicity profile

- Caveat: Each patient experiences therapy differently

The Package Insert: Not the Full Story

- Data from clinician reporting in addition to pharmacokinetics, drug interactions, safety warnings
 - Indirect method increases risk of errors in interpretation of effect of adverse event
 - Likely underestimates frequency and severity of adverse events from patient perspective
 - May misrepresent “tolerability” but accurately present “safety”



Issues with Adverse Event Reporting

- Approximately 10% of CTCAE items are subjectively assessed
 - Low level of inter-investigator reliability
- Majority of patients report ≥ 1 symptom
 - At least 1 symptom “frequent, severe, and/or interfering “quite a bit” with daily activities
- Clinician-reported toxicity has low concordance with patient’s overall health status
 - Clinicians underreport prevalence and severity of symptoms
 - Patients typically report higher grade and earlier onset
 - Greatest difference: reporting adverse events that correlate with daily life and quality of life

Di Maio M et al, Nature Reviews Clinical Oncology 2016

Basch E et al, JAMA Oncology 2017

Dueck AC et al, JAMA Oncology 2015

Di Maio M et al, J Clin Oncol 2015

Why the Discrepancy in Reporting?

- Clinician factors:

- Difficult to quantify subjective symptoms
- Pay less attention to mild symptoms
- Burden of documentation
- Toxicities “expected” or routine
- Symptoms deemed unrelated to treatment
- Do not ask about unusual or unexpected toxicities
- Time limitations during visit



- Patient factors:

- Do not want to report toxicities that might risk removal from drug/treatment
- Do not think expected toxicities need to be reported
- Risk:benefit ratio favors staying on treatment
- Recall of symptoms declines with time



Patient-Reported Adverse Event Monitoring

- Capture the patient experience
 - Done in real-time with direct questions
 - An unfiltered reflection of the patient's experience
- Adherence declines over time
 - Systematic issues—staff forgot to administer, technology does not work
 - Patient factors—feeling too ill at visit, no longer interested in reporting
- Discrepancies between investigator reporting and patient report
 - Investigators consistently report lower grades
 - Greatest discrepancies in subjective effects
 - Delay in reviewing patient report or did not use to evaluate adverse events

Conclusions

- Safe therapies are not always tolerable
 - If patients will not take the treatment due to side effect burden interfering with lifestyle or quality of life, the treatment is ineffective
- Current clinical trial adverse event reporting does not tell full story
- Assessment of tolerability is complex
 - Patients and clinicians will overlook/minimize toxicity if treatment is improving cancer burden
 - Clinician-reported toxicity alone cannot and does not tell the full story
 - Patient-reported adverse events may complete toxicity profile (day to day experience)
- Therapies need to be safe AND tolerable in order to be effective

Safety vs Tolerability

The Canadian Regulatory Perspective

Katherine Soltys, M.D.

Acting Director, Bureau of Medical Sciences

Therapeutic Products Directorate, Health Products and Food Branch

Health Canada



Outline

- Health Canada Regulations and Guidance that reference safety and tolerability as applied to oncology products
- Health Canada regulatory approach to incorporating the patient perspective in regulatory reviews and labelling
- Future perspectives

Regulations

- **Health Canada's Health Products and Food Branch (HPFB)** is the national regulatory authority responsible for evaluating and monitoring the quality, safety, and efficacy of therapeutic products in Canada
- **Food and Drugs Act and Regulations**
 - Division 5: Drug Development (Clinical Trials) – efficacy, safety, ethics, GCP
 - Division 8: New Drugs - Notice of Compliance – “...*new drug submission (or supplement to) complies with the requirements of sections C.08.002 and C.08.005.1 of the Food and Drug Regulations. Pursuant to section C.08.004 of the Food and Drug Regulations, this Notice of Compliance is issued*”

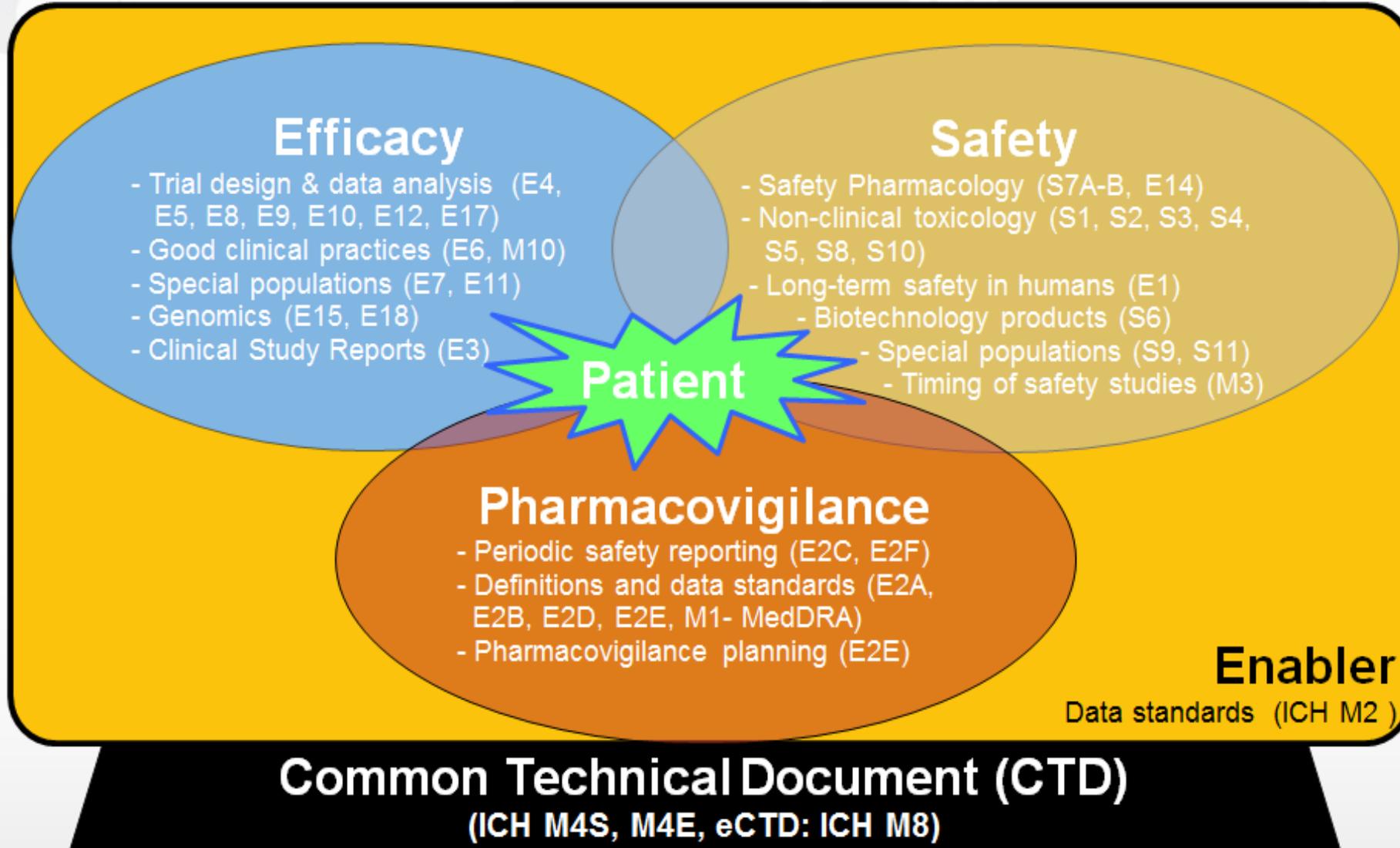
Regulations

- Submission shall contain sufficient information to enable the Minister to assess the **safety and effectiveness** of the new drug, including:
 - Detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended
 - Substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended
 - Quality – manufacturing, ingredients, potency, purity, stability, safety of the new drug

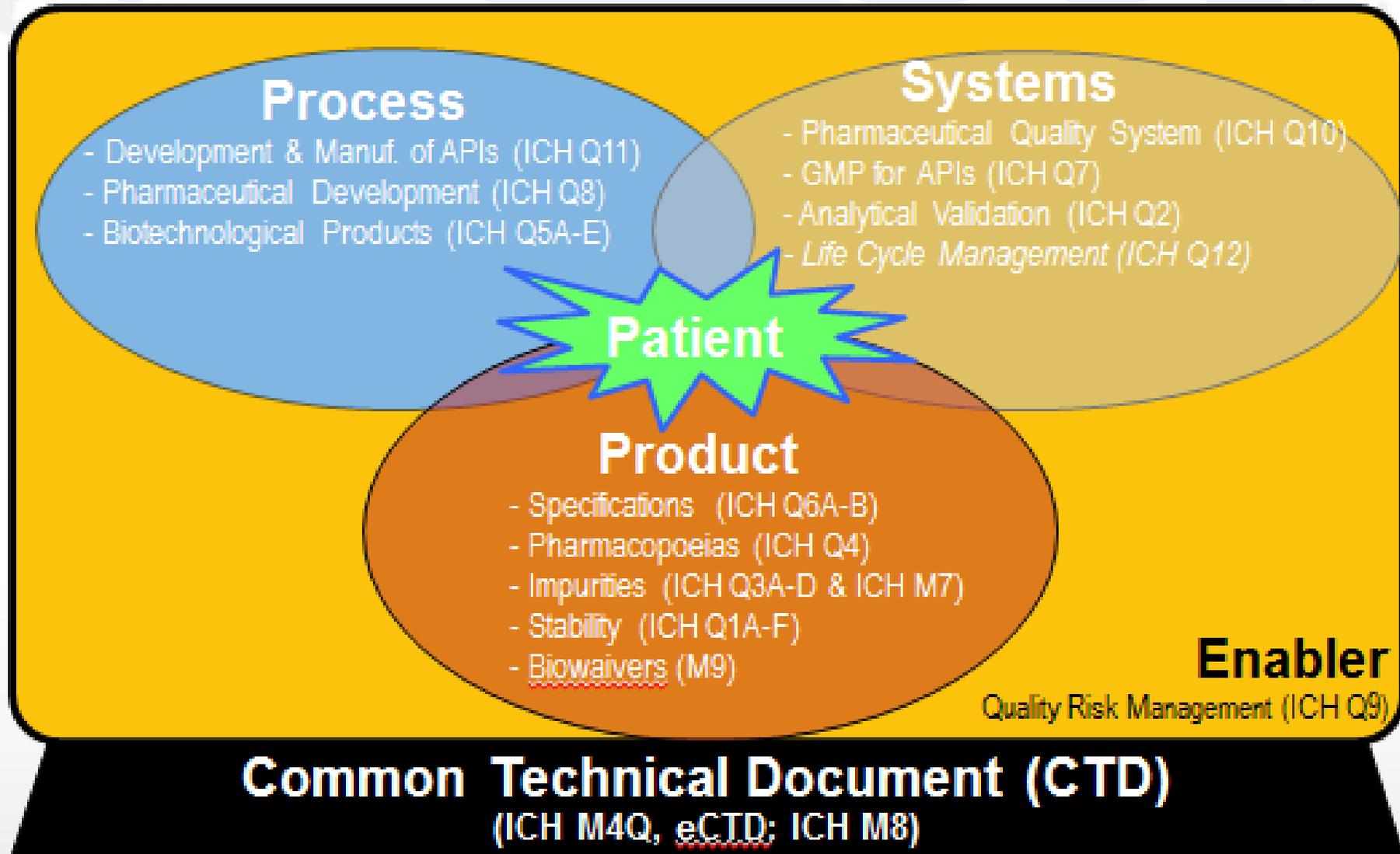
Guidance

- **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**
 - Safety: carcinogenicity; genotoxicity; reproductive toxicity; assessment of QT interval prolongation liability
 - Efficacy: design, conduct, safety, and reporting of clinical trials; novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines
- **Health Canada Guidance** (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/index-eng.php>)
 - Notice of compliance with conditions
 - Priority review of drug submissions
- **International Guidance**
 - FDA
 - EMA – eg. Guideline on the evaluation of anticancer medicinal products in man; Appendix 2 The use of patient-reported outcome measures in oncology studies

ICH E- and S-Guidelines



ICH Q-Guidelines



ICH E9 Statistical Principles for Clinical Trials

- “The **safety** of a medical product concerns the medical risk to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and haematology), vital signs, clinical adverse events (diseases, signs and symptoms), and other special safety tests (e.g. ECGs, ophthalmology).”
- “The **tolerability** of the medical product represents the degree to which overt adverse effects can be tolerated by the subject.”

Regulatory Safety Assessment

- Median duration of therapy
- Adverse events (on treatment and within 30 days of last dose)
 - Symptomatic; Abnormal hematologic and clinical chemistry findings
 - CTCAE all-grades; grades 3 and 4
 - Serious
 - Leading to discontinuation
 - Requiring dose interruption or change
 - Leading to hospitalization
 - Requiring additional therapy
- Deaths (on treatment and within 30 days of last dose)
- This information goes into Product Monograph (Box warning, etc.)

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

- Descriptive terminology used for AE reporting; organized by SOC (highest level of MedDRA hierarchy)
- AE (sign or symptom) that may or may not be related to the drug
- Grade 1 – Mild; no intervention indicated
- Grade 2 – Moderate; minimal intervention is required
- Grade 3 – Hospitalisation; severe; not immediately life-threatening
- Grade 4 – Life-threatening; urgent intervention indicated
- Grade 5 – Death related to AE

Case Example #1: Safety vs. Tolerability

EGFR TKI			Placebo	
NCI-CTC Grade	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
MedDRA Preferred Term	%	%	%	%
Rash	49	6	6	0
Diarrhea	20	2	4	0
Fatigue	9	2	6	1
Anorexia	9	<1	5	<1
Pruritis	7	<1	3	0
Dry Skin	4	0	1	0
Weight Decreased	4	<1	<1	0
Paronychia	4	<1	0	0

Regulatory Tolerability Assessment

- The **tolerability** of the medical product represents the degree to which overt adverse effects can be tolerated by the subject (ICH E9)
- How do we measure tolerability?
 - Death
 - Treatment discontinuations or dose interruptions/reductions
 - Use of supportive therapies
 - Hospital admissions

Case Example #2: Safety vs. Tolerability

	Study Drug		Comparator	
	All Grades	Grades 3 & 4	All Grades	Grades 3 & 4
Deaths	25		20	
AEs (drug-related)	95%	60%	75%	10%
SAEs (drug-related)	7%	7%	2%	2%
AEs leading to discontinuation	13%	9%	1%	0.5%
AEs requiring dose interruption or change	70%	50%	8%	3%
AEs requiring additional therapy	60%	20%	40%	5%

Patient Perspective

- Recognition that a patient's symptoms or function are important
- What is the best way to capture the patient perspective?
- Patient reported outcomes are rarely included in labelling
 - High rate of missing data
 - Infrequent assessments
 - Poor content validity (i.e. the instrument does not measure what it was intended to measure)
- What should be measured?
- How should it be measured?
- Was statistical testing done and was it pre-specified?

Future Perspectives

- Inclusion of patient experience data in the drug development process can lead to better-informed regulatory decisions that benefit patients
- A benefit in a patient reported outcome measure could be used to support an efficacy endpoint such as Progression Free Survival or Response Rate
 - Fewer oncology trials have Overall Survival as primary efficacy endpoint ('live longer')
 - Can a trial demonstrate improvement in an endpoint that is important to patients? ('live better')
- Patient reported outcome data to support comparative safety and tolerability

Summary

- Safety ≠ Tolerability. While product labelling summarises safety data from the registration trials, useful information about tolerability often remains elusive
- Better tolerability data in product labelling (meaningful to patients) would help inform patients and healthcare providers during treatment option discussions
- Traditional data collection mechanisms exist but we need to incorporate the patient voice in drug development to improve the regulatory decision making process and ultimately the real-world patient experience

Patient Advocate and Survivor

Karen E. Arscott, DO, MSc

Associate Professor of Medicine-Patient Advocate and Survivor

Geisinger Commonwealth School of Medicine



Panel Discussion and Q & A

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