ICH
harmonisation for better health

MedDRA in clinical trials – industry perspective

SFDA-ICH MedDRA Workshop, Beijing, 13-14 May 2011

Christina Winter, MD, FFPM
Medical director
GlaxoSmithKline R&D / ICH MedDRA Management Board

©2011 ICH

Disclaimer:

- **The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.**

© 2011 ICH

Applications of MedDRA

Numerous applications including:

- **Indications for treatment**
- **Medical history**
- **Adverse events, Serious adverse events**
- **Investigation/test results**
- **Procedures**

© 2011 ICH

Training and standard operating procedures

- **Train**
  - Investigators and clinical research organisations
  - Within company: clinical coding team, data management, statisticians, clinical study team, pharmacovigilance
  - Later stages of development: staff responsible for product labelling
- **Standard operating procedures/working practices**
  - Align with ICH MedDRA Points to consider documents
    - 'Term selection' and 'Data retrieval and presentation'
  - Align with regional regulatory requirements

© 2011 ICH

Clinical trials - data entry

- **Reporter verbatim text for AEs/SAEs obtained from case report forms (paper or electronic)**
- **“Synonym list” (if used) makes autoencoding of reporter verbatim more efficient and consistent**
- **Autoencoder failures are manually coded**
- **Queries sent to reporting investigator as needed**
  - Ambiguous text
  - Clarify events: Is ‘severe anaemia due to wrist cutting’ a report of two events or a suicide attempt?

© 2011 ICH

Quality assurance - examples

- **Autoencoded terms are manually checked**
- **Manual coding: one dictionary analyst codes, another checks/approves**
- **Clinical trial team sees all coded terms and reporter verbatim (unique term report) during study monitoring**
  - Unique term report is included in study file

© 2011 ICH

Synonym lists – used by some companies

“ Clean” verbatim text saved as synonym for future use

- Aids the autoencoder
- Improves consistency of coding
- Company specific: Not part of MedDRA

Synonym	LLT	PT
Progressive headache	Headache aggravated	Headache
Worsening episodic headache	Headache aggravated	Headache
Light pressure on head	Head pressure	Headache
Head pressure in the morning	Head pressure	Headache

© 2011 ICH

Unique term report – partial view
(full view contains hierarchy up to SOC)

AE verbatim text	LLT_NAME	PT_NAME
ANEMIA	Anemia	Anaemia
DEATH FROM CORONARY ARTERIOSCLEROSIS POST TRIAL	Arteriosclerosis coronary artery	Arteriosclerosis coronary artery
SLIGHT CARDIAC RHYTHM DISTURBANCE BRADYCARDIA	Bradycardia	Bradycardia
HEART FAILURE {DEATH}	Cardiac failure	Cardiac failure
STABBING HEART	Cardiac pain	Angina pectoris
CARDIOGENIC SHOCK	Cardiogenic shock	Cardiogenic shock
FIRST DEGREE ATRIOVENTRICULAR BLOCK ON ECG	First degree atrioventricular block	Atrioventricular block first degree
FLUTTERY FEELING IN CHEST	Heart fluttering	Cardiac flutter
HEART FLUTTERING FEELING	Heart fluttering	Cardiac flutter

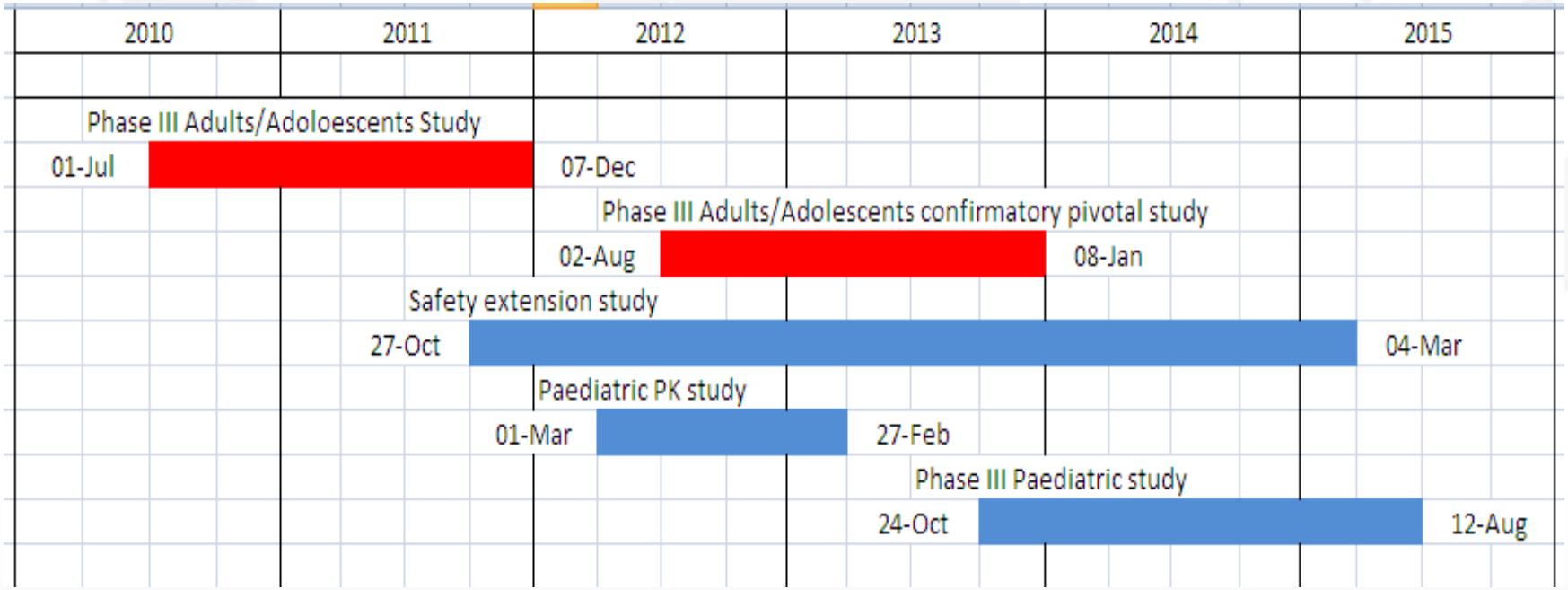
© 2011 ICH

MedDRA Version changes

- **6 monthly version changes**
- **Update of electronic reporting database is synchronised with regulators (e.g. EU)**
  - First Monday of second month after new version release
- **Process is company specific: *examples***
  - Relink synonyms to new LLTs. Clinical and postmarketing data upversions at the same time as relinks are taken off common IT platform overnight
  - Recode data by product or active study

© 2011 ICH

Clinical trials: overlap several MedDRA versions



© 2011 ICH

Version changes – clinical trials

- Six suggestions on MSSO web page
- Industry prefers freedom of choice
- Clear descriptions in study reports/marketing application of what has been done
- Clear explanation of any impact of MedDRA version on potential safety signal in the Integrated Safety Summary

© 2011 ICH

Version changes – clinical trials (2)

Options 1 – 3

- **Freeze at start of project, report with same version**
- **Freeze at start of project, report with latest version**
- **Freeze at initiation of each trial within project and report with latest version**

© 2011 ICH

Version changes – clinical trials (3)

Options 4 - 6

- **Hold all coding till end of each trial; recode all studies at the end of project**
- **Freeze at start of trial & optionally recode with the latest version at conclusion of trial using criteria defined in the project plan**
- **Do not freeze; recode data for all trials in project on an ongoing basis with the latest version**

© 2011 ICH

Clinical trials – data output

- **Traditional review of tables or may use electronic tool(s) in addition**
  - PTs shown by incidence
  - PTs arranged by primary SOC
  - PTs shown by secondary SOC
  - Apply SMQs (as appropriate)
  - Statistical analysis (signal detection in larger data sets)
- **Company or compound specific**
  - Alerts for events of interest (monitored list)

© 2011 ICH

Clinical trials - single study, most common AEs

Preferred term	Placebo (n=54)	Study drug (n=54)
Headache	10 (19%)	11 (20%)
Dizziness	3 (6%)	6 (11%)
Nausea	2 (4%)	4 (7%)
Vomiting	2 (4%)	3 (5%)
Diarrhoea	3 (5%)	1 (2%)
Nasopharyngitis	5 (9%)	6 (11%)
Fatigue	0	2 (4%)
Rash	3 (6%)	1 (2%)
Hypersensitivity	0	2 (4%)*
*Verbatim: Allergy symptoms		

© 2011 ICH

Primary SOC analysis

Adverse Event (MedDRA v14.0)	25 mg MyDrug (N=44)	Placebo (N=15)
SOC Infections and infestations	14 (31.8%)	4 (26.7%)
PT Upper respiratory tract infection	5	2
PT Sinusitis	3	0
PT Urinary tract infection	2	1
PT Ear infection	2	0
PT Viral infection	2	0
PT Bronchitis	1	0
PT Influenza	1	0
PT Localised infection	0	1
PT Lower respiratory tract infection	1	0
PT Pneumonia	1	0
PT Tooth abscess	1	0

© 2011 ICH

Secondary SOC - the same data

Adverse Event (MedDRA v14.0)	25 mg MyDrug (N=44)	Placebo (N=15)
SOC Respiratory, thoracic and mediastinal disorders		
PT Upper respiratory tract infection	5	2
PT Sinusitis	3	0
PT Bronchitis	1	0
PT Influenza	1	0
PT Lower respiratory tract infection	1	0
PT Pneumonia	1	0
SOC Infections and infestations		
PT Viral infection	2	0
PT Localised infection	0	1
SOC Renal and urinary disorders		
PT Urinary tract infection	2	1
SOC Ear and labyrinth disorders		
PT Ear infection	2	0
SOC Gastrointestinal disorders		
PT Tooth abscess	1	0

© 2011 ICH

Analysis with SMQs

- **Gathers data including events from SOCs that do not have secondary links, e.g. *Investigations***
- **Explore clinical trial data for known safety issue e.g. compound class effect**
- **Explore clinical trial data for potential safety issue - signal seen in pre-clinical studies**

© 2011 ICH

Special tools

- **Not part of MedDRA subscription but available from vendors**
- **Examples in following slides:**
  - Used by some companies and regulators for post marketing signal detection
  - Also applied to clinical data by some companies

© 2011 ICH

Clinical trials – Single study, AEs by primary SOC

			Treatment (N=39)		Comparator (N=12)		Total (N=51)	
Body System	Adverse Event		#	%	#	%	#	%
Eye disorders	Conjunctivitis		1	2.6%	0	0%	1	2%
Eye disorders	Ocular hyperaemia		2	5.1%	0	0%	2	3.9%
Eye disorders	Pterygium		1	2.6%	0	0%	1	2%
Eye disorders	Vision blurred		2	5.1%	0	0%	2	3.9%
Gastrointestinal	<Any Event in Gastrointestinal disorders>		9	23.1%	3	25%	12	23.5%
Gastrointestinal	Abdominal discomfort		1	2.6%	0	0%	1	2%
Gastrointestinal	Abdominal pain		1	2.6%	0	0%	1	2%
Gastrointestinal	Aphthous stomatitis		1	2.6%	0	0%	1	2%
Gastrointestinal	Constipation		1	2.6%	0	0%	1	2%
Gastrointestinal	Diarrhoea		0	0%	1	8.3%	1	2%
Gastrointestinal	Dry mouth		2	5.1%	0	0%	2	3.9%
Gastrointestinal	Dyspepsia		1	2.6%	0	0%	1	2%
Gastrointestinal	Epigastric discomfort		2	5.1%	0	0%	2	3.9%
Gastrointestinal	Hypoaesthesia oral		1	2.6%	0	0%	1	2%
Gastrointestinal	Nausea		2	5.1%	2	16.7%	4	7.8%
Gastrointestinal	Vomiting		2	5.1%	2	16.7%	4	7.8%

© 2011 ICH

Statistical analysis – signal detection in larger data sets

Kind of Analysis

Analysis Group: AEs **Analysis Type:** MedDRA PT

Population Subgroups

Sex: All **Age Group:** All **Race:** All

Columns and Rows Print Download View Sector Map

Rows are filtered

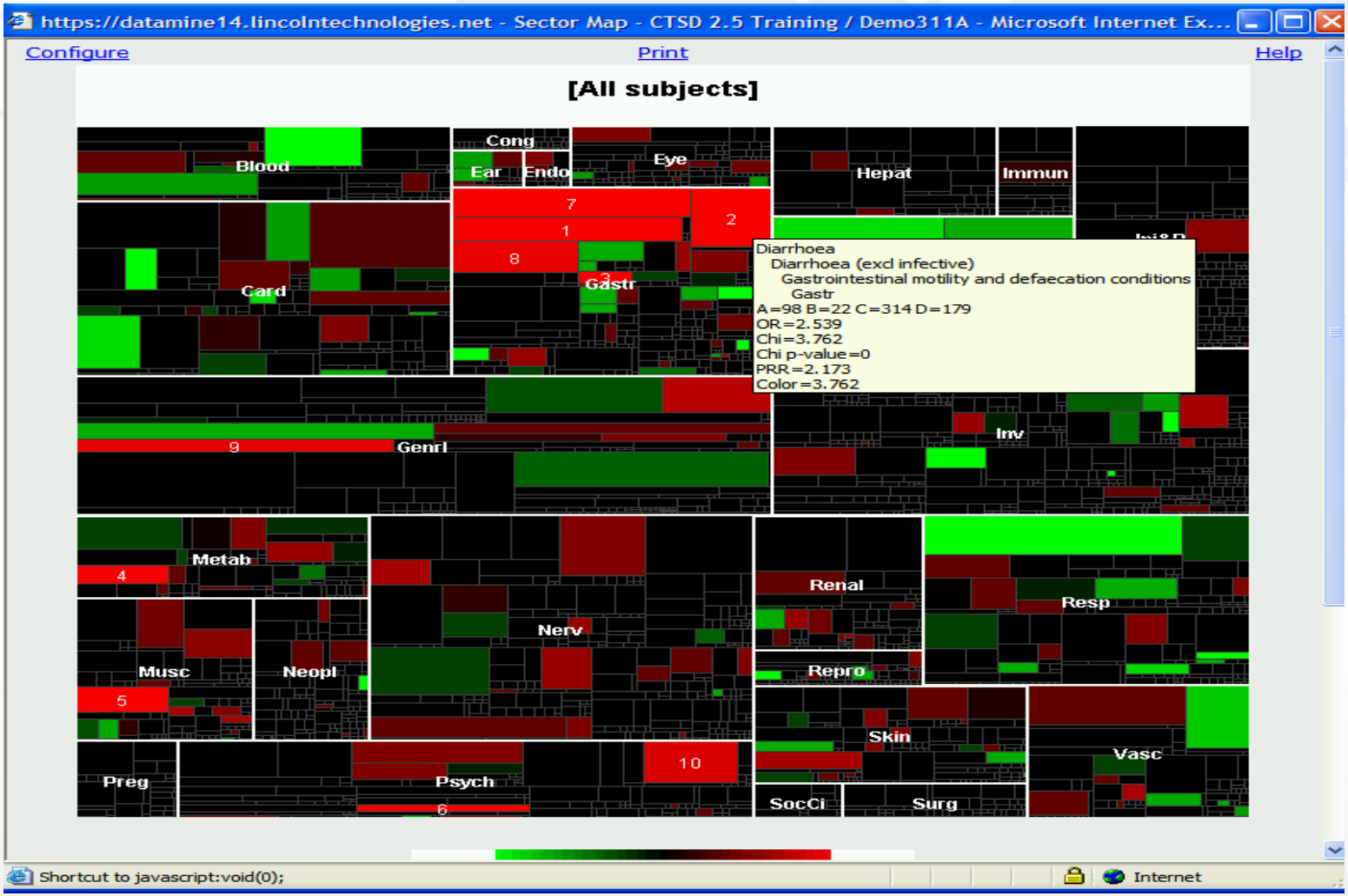
271 rows Sorted by SCORE

Rows Per Page: 25 Page 1 of 11

ISSUE	TYPE	SCORE	CHI	ODDS_RATIO	OR025	SEX	AGE_GROUP	RACE	A	B	N_T	N_C
Nausea	PT	0.000002	4.617	4.227	2.197	All	All	All	81	11	412	201
Diarrhoea	PT	0.000084	3.762	2.539	1.544	All	All	All	98	22	412	201
Dyspepsia	PT	0.001260	3.021	3.107	1.439	All	All	All	47	8	412	201
Anorexia	PT	0.002684	2.784	10.204	1.360	All	All	All	20	1	412	201
Arthralgia	PT	0.002684	2.784	10.204	1.360	All	All	All	20	1	412	201
Insomnia	PT	0.003200	2.727	4.629	1.387	All	All	All	27	3	412	201
Vomiting	PT	0.019082	2.073	2.168	1.027	All	All	All	38	9	412	201
Abdominal pain	PT	0.026968	1.927	1.665	0.987	All	All	All	67	21	412	201
Pain	PT	0.033028	1.838	3.015	0.878	All	All	All	18	3	412	201
Depression	PT	0.042777	1.719	100000000.000	??	All	All	All	6	0	412	201
Infection	PT	0.042777	1.719	100000000.000	??	All	All	All	6	0	412	201
Fatigue	PT	0.068583	1.486	2.250	0.751	All	All	All	18	4	412	201

© 2011 ICH

Sector Map



© 2011 ICH

Clinical trials- expedited SAE reporting

- **Electronic reporting is possible if database is compatible with regulators**
- **MedDRA used for**
  - AE field, drug indications, medical history, investigations, cause of death
    - Refer to ICH E2B (R2) for details of Individual Case Safety Reports (ICSRs)
- **Physical appearance of report may be similar to CIOMS 1 reports for spontaneous data**

© 2011 ICH

CIOMS 1 - Expedited report

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 2)

Protocol No:

Eudract No:

Subj. ID: Treat. No:

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
	Argentina				30Mar

8. - 12. CHECK ALL APPROPRIATE TO EVENT

7. & 13. DESCRIBE EVENT(S)

Convulsion

This -year-old subject was enrolled in a study conducted by Argentina for the treatment of moderate papulopustular facial rosacea. The subject was randomized to placebo. Medical conditions at the time of the event included addiction to heroin and a past history of drug abuse. This was not disclosed to the site at study entry. Other history included panic attacks, hypertension, and anxiety. Concomitant medications included

. The subject received from an unspecified date in 1996 for treatment of depression, and from an unspecified date in 1990.

On March , approximately five years after commencing treatment with , the subject experienced a "seizure" with loss of consciousness while in a pharmacy. was taken to the emergency room where reported had experienced shaking of the

- ☐ PATIENT DIED AS OUTCOME OF EVENT
- ☐ RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☒ CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- ☐ OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S)

20. DID EVENT ABATE AFTER STOPPING DRUG?

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION
Unknown	Oral

☒ YES ☐ NO ☐ N/A

17. INDICATION(S) FOR USE

DEPRESSION

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

© 2011 ICH

CIOMS 1 – Expedited report

Coding of medical history on report form

MEDICAL CONDITION	START DATE	END DATE	CONTINUING
DRUG ABUSE	Unknown	Unknown	Unknown
DRUG ADDICT	Unknown	Unknown	Unknown

© 2011 ICH

Clinical study reports (on study completion)

- **Industry provides to regulators in countries where study has been conducted**
- **Safety data presented has been "processed"**
  - Reports commonly include
    - tables of most common events (PTs primary SOC)
    - tables of events considered related to drug (PTs primary SOC)
    - other analysis (e.g secondary SOC, SMQ) may be provided (dependent on drug, size of dataset, stage of drug development etc)
    - may include appendix of verbatim to LLT links if there are any unusual terms

© 2011 ICH

Clinical investigator brochure (IB)

- **Provided to regulator with clinical study application (CTA)**
- **For new chemical entity 'first time in man' study, IB has in-vitro and animal data only**
- **IB updated at end of each completed clinical study**
- **Includes:**
  - Tables for most common adverse events (MedDRA PTs) for each study
  - Draft label (Developmental core safety information, DCSI) after several studies have been completed

© 2011 ICH

Other information: industry to regulator

- **Requirements vary across regions**

Example:

- **EU Annual Safety Reports (ASRs) for Clinical Trials**
  - For each drug
    - description of new key safety issues for project (e.g. protocol revisions for safety reasons)
    - Includes newly identified adverse reactions*
    - ICH line listing for suspected serious adverse drug reactions*
    - Summary table of suspected serious adverse drug reactions*

**MedDRA PTs*

© 2011 ICH

Example of line listing

System Organ Class	Protocol Id + Eudract Number	Case Id + Subject Number	Country Of Reporter	Age + Gender	Events	Listedness	Outcome	Date Of Onset + Time To Onset + TTO SLD	Drug + Route + Formulation+ Total Daily Dose	Dose Started	Dose Stopped
Nervous system disorders	Protocol X 2006-xxxxxx-20	B0XXXXXXA 1026	Germany	37 Years Female	Multiple sclerosis relapse	Not assessed	Resolved	07May2009 338 Days 168 Days	Drug A Oral 1800 mg	03Jun2008	20Nov2008
	Protocol X 2006-xxxxxx-20	B0XXXXXXA 302	Germany	31 Years Female	Muscle spasticity	Unexpected	Resolved	07Jan2008 87 Days 5 Days	Drug A Oral 1200 mg	12Oct2007	02Jan2008

© 2011 ICH

Information provided to investigators

- **All investigators have the latest IB**
- **Additional information provided varies by region**

Example

- EU: periodic safety reports for investigators
  - Contains line listing (MedDRA PTs) for serious unexpected related reactions

© 2011 ICH

At time of marketing application

- **ICH Common Technical Document (CTD) and e-CTD**
  - Format for new drug and biologic product applications to regulatory authorities with coding of adverse events in the clinical section
  - Contains Integrated safety summary (ISS) with adverse events from pivotal studies
    - ISS produced by company statistician from criteria agreed by clinical submission team.
    - ISS used to update draft product label

© 2011 ICH

Example of CTD table

Incidence of Adverse Events in Individual Studies						
	Reported incidence by Treatment Groups					
SOC / Adverse event	Study X			Study Y		Study Z
	Drug X 60mg bid N=104	Drug x 30mg bid N=102	Placebo N=100	Drug x 60mg bid N=200	Drug Y 100mg qid N=200	Drug X 60mg bid N=800
Nervous system disorders						
Headache	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gastrointestinal disorders						
Nausea	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Vomiting	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Flatulence	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

© 2011 ICH

Risk management plans (RMP)

- **Agreed within company during clinical development**
- **Includes potential safety issues**
  - e.g. Issues from pre-clinical programme, from compounds with similar pharmacology (class of compound), etc
  - May have agreed list of MedDRA terms for each medical concept being monitored
- **At time of marketing application, plan for continued monitoring after marketing is agreed with regulators**
  - Issues identified by the Marketing Application Holder (company) and agreed by the regulator

© 2011 ICH

RMPs (2)

- **EU risk management plans request MedDRA terms and codes for items perceived as risk for the marketed product.**
  - May be any level of MedDRA hierarchy
  - May include SMQs
- **Post marketing RMP list updated by the company; communicated at intervals to regulator (e.g. with PSURs)**
- **Common understanding and coding terminology makes risk monitoring more efficient**

© 2011 ICH

MedDRA for labelling

- **The labelling process**
  - Emerging safety profile (from each completed study)
  - Developmental core safety information (DCSI)
  - Label at time of marketing application
    - Company Global data sheet/ local product label
- **Examples**
  - Draft label
  - Regional differences in marketed product labelling
    - EU label
    - US label

© 2011 ICH

Emerging safety profile

Early phase clinical studies

- **Adverse events (MedDRA PTs) displayed by incidence for each study**
- **Most common AEs, dose related AEs from each study**
- **Recurring AEs in more than one study**
- **Decision to create draft label (developmental core safety information) when there is sufficient data**

© 2011 ICH

Developmental core safety information

- **Team may include: statistician, project physician, safety physician etc**
- **Review of aggregated data from several studies**
  - Emerging pattern of most common AEs (MedDRA PTs) at greater incidence than placebo
  - Emerging pattern of AEs that may be dose related
  - Consider combining incidence for similar PTs
    - e.g. *Insomnia, Initial insomnia, Middle insomnia*
- **Draft label placed in investigator brochure**
  - To inform investigators
  - Guide sponsor's expectedness assessments for SAEs

© 2011 ICH

Example: table used to create draft label

Treatment Emergent Adverse Events
Incidence of at Least 5% in Any Dose Group (12-Week Controlled Studies)

Preferred Term	Number (%) of Subjects				
	Placebo (N=245)	XX 600mg (N=163)	XX 1200mg (N=269)	XX 1800mg (N=38)	XX 2400mg (N=45)
Any event	**182 (74)**	**132 (81)**	**226 (84)**	**32 (84)**	**44 (98)**
Somnolence	12 (5)	32 (20)	61 (23)	10 (26)	23 (51)
Dizziness	11 (4)	22 (13)	59 (22)	10 (26)	18 (40)
Headache	28 (11)	19 (12)	41 (15)	4 (11)	6 (13)
Nasopharyngitis	17 (7)	14 (9)	21 (8)	3 (8)	2 (4)
Nausea	12 (5)	9 (6)	18 (7)	3 (8)	3 (7)
Fatigue	11 (4)	9 (6)	18 (7)	1 (3)	2 (4)
Dry mouth	5 (2)	5 (3)	12 (4)	2 (5)	4 (9)
Irritability	3 (1)	6 (4)	11 (4)	2 (5)	2 (4)
Diarrhea	12 (5)	6 (4)	10 (4)	2 (5)	2 (4)

© 2011 ICH

Label at time of marketing application

- **At time of marketing application**
  - Review integrated safety summary of studies for the submission
  - Consider label of any similar marketed products (e.g. different formulation or pro-drug)
  - Draft label converted to company's Global datasheet (GDS) with core safety information.
    - ADRs that company considers related to drug
    - Core safety information is reflected in all local labels
  - Final "local" label agreed with regulatory agency
  - GDS and local label commonly use MedDRA PT level

© 2011 ICH

ICH
harmonisation for better health

Thank You!

©2011 ICH