FDA Medical Queries (FMQs)

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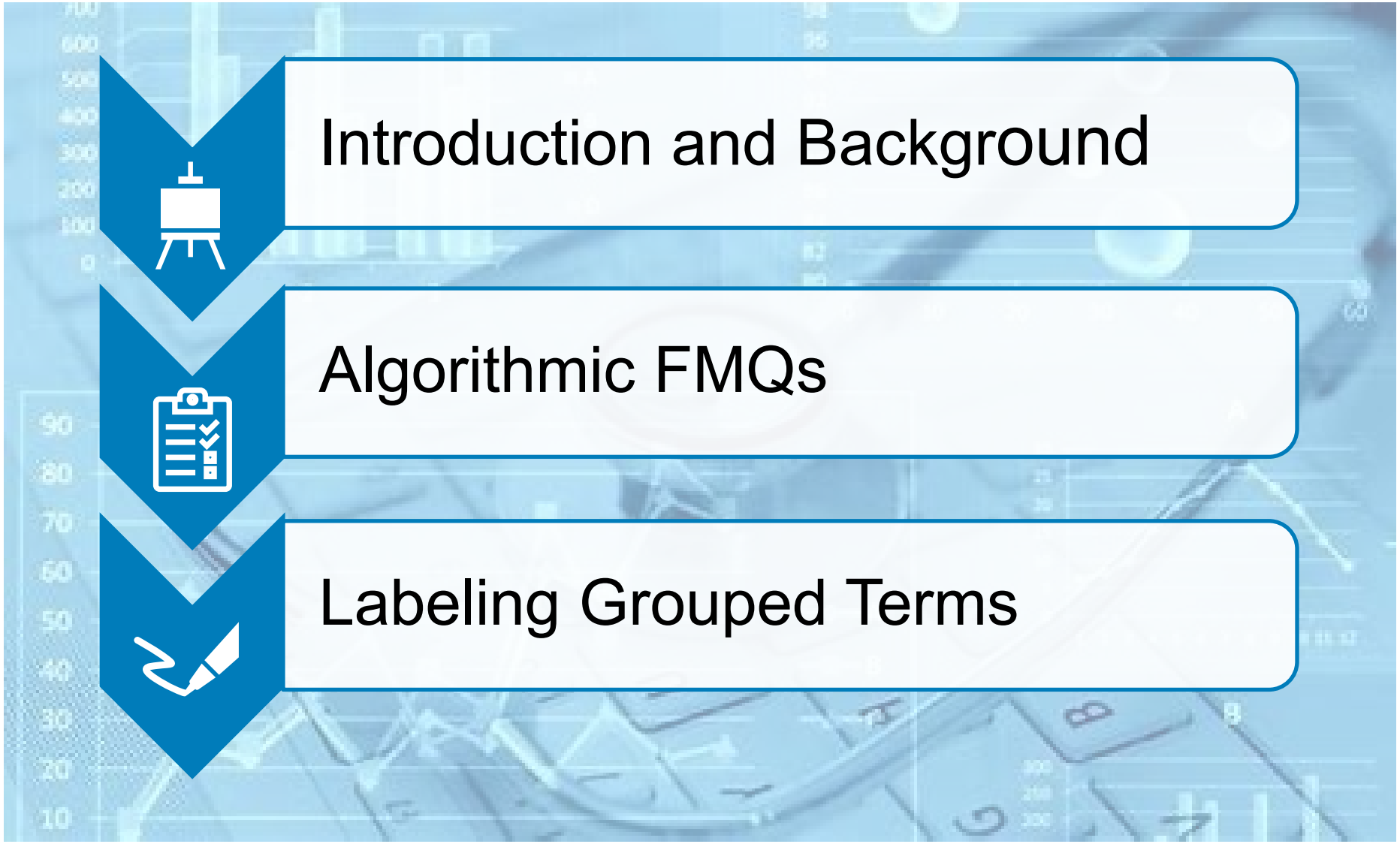
Agenda


Introduction and Background
Algorithmic FMQs
Labeling Grouped Terms

Why FDA Medical Queries?

Inconsistent Standards

- Investigators may report different verbatim terms for similar clinical events, resulting in varying coded MedDRA preferred terms for the same medical concept
  - A patient complaining of abdominal pain may be reported using verbatim terms coding to abdominal pain, abd. pain lower, abd. pain upper, gastrointestinal pain, visceral pain, abdominal discomfort, among others
- Adverse Events (AEs) may manifest in related, but different ways.
  - A patient with a rash related to drug hypersensitivity may present with an erythematous rash, a macular rash, a macular-papular rash, a papular rash, a morbilliform rash, etc., and each would be coded to a different PT
- When **related** PTs are not grouped, it's **possible to miss** important safety signals.

FDA Medical Queries

A Collective Way Forward

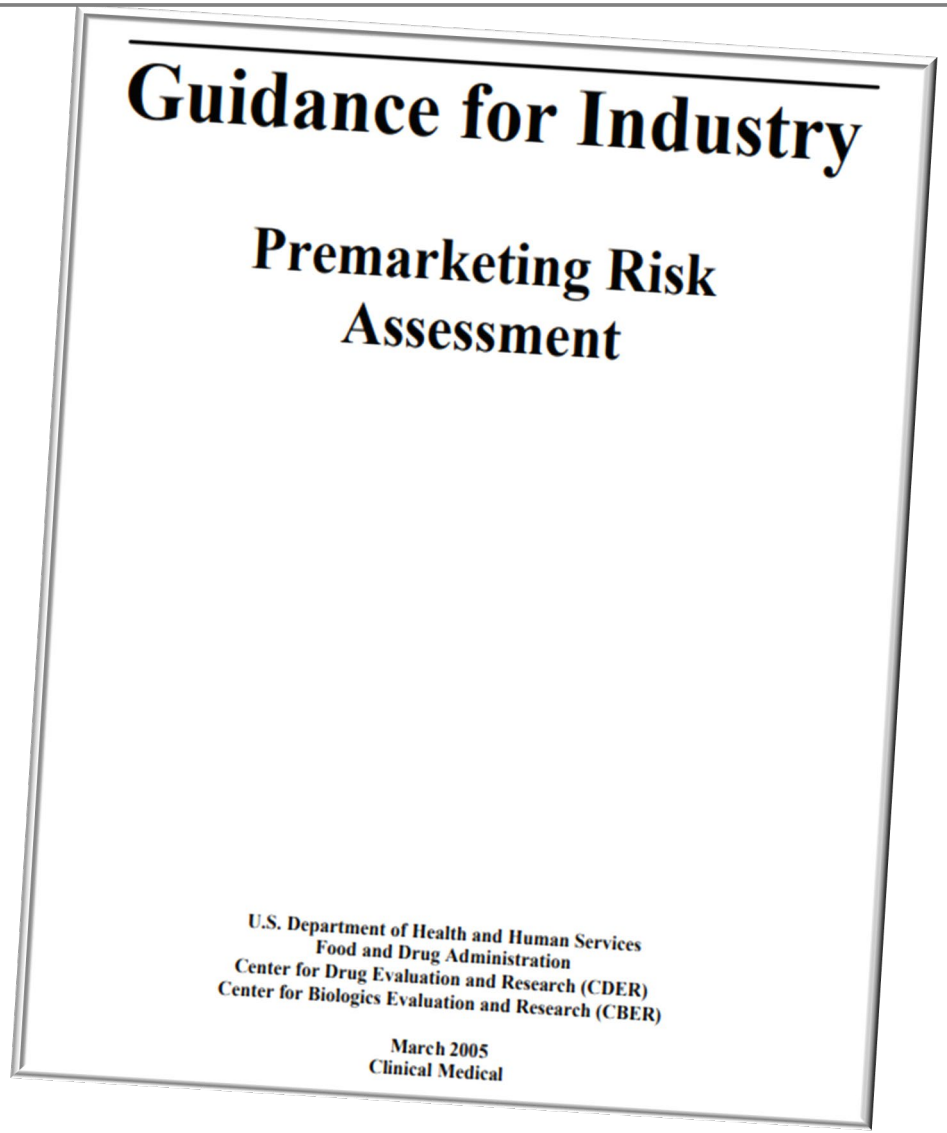
- Used natural language processing to determine most frequently encountered terms found in >38,000 labels of 1,254 active moieties
- Received requests from review divisions
- Evaluated existing queries
- Established the FMQ Working Group and collaborated with 80 reviewers across Divisions

An OND Standard

- Launched 104 FMQs
- Includes 4 Algorithmic FMQs
- Recommendations for FMQ labeling

OND= Office of New Drugs

Importance of Grouping Similar PTs Not a New Concept

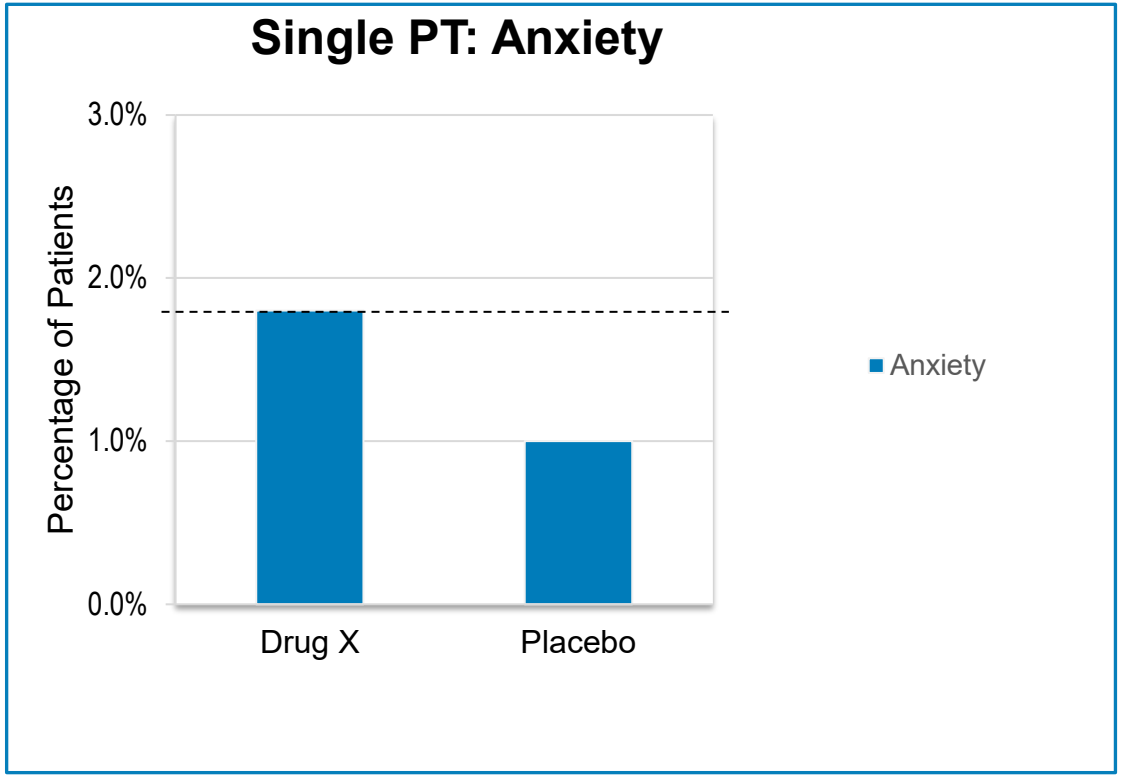


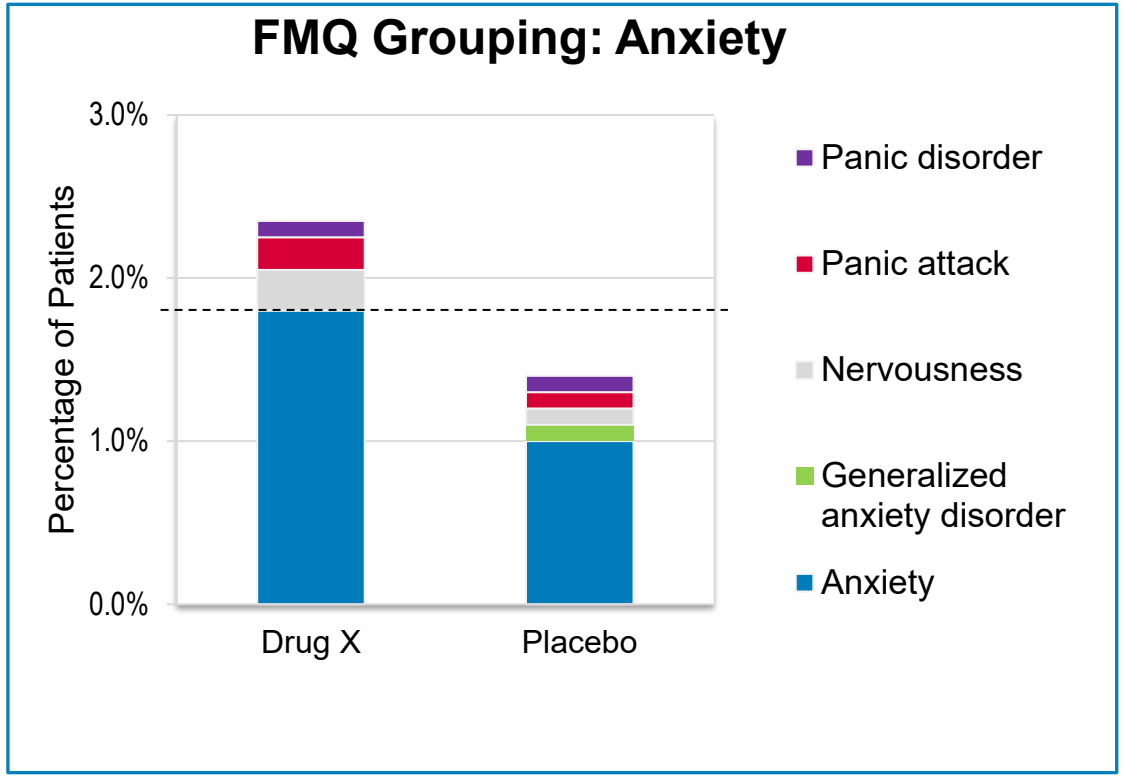
What are FMQs?

- Standardized groupings of related PTs developed by review staff primarily in FDA/CDER.
- MedDRA PTs are highly granular with >24000 PTs
- Each grouping represents a medical concept.
  - Example: “Initial insomnia,” “middle insomnia,” “early morning awakening,” combined to “insomnia.”
- Goal is to improve safety signal detection in clinical trial datasets.
- Standardized approach to increase efficiency and consistency.

Single PT Analysis vs. FMQ Grouping

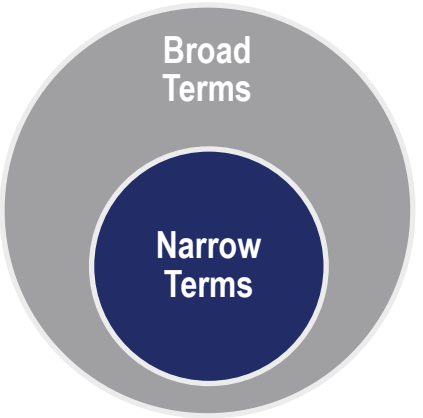
- Using a 2% cut-off for an AE analysis, “Anxiety” doesn’t make the cut, but group these PTs, and a signal emerges at the 2% cut-off (no patient counted twice).

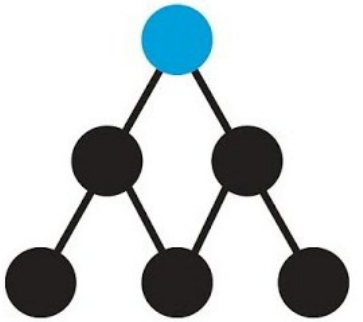




FMQ Concepts
Narrow vs. Broad vs. Algorithmic Queries

- Narrow FMQ terms:
  - Specific for the medical concept
  - Indicate that the FMQ occurred, More than ~90% probability
- Broad FMQ terms:
  - “Cast a wider net” than narrow query terms for signal detection
  - Less specific
  - Provide reasonable assurance (more than ~30% probability) that the medical concept occurred
- Algorithmic FMQs
  - Uses data from the laboratory, Concomitant medications, medical history datasets in addition to the AE datasets
  - Uses temporal associations





FMQ Ground Rules: Narrow Queries

Narrow Queries: Indicates FMQ concept occurred

- PTs that are near-synonyms of the FMQ concept
  - PT Abdominal Discomfort in FMQ Abdominal Pain
- PTs that are subgroups of the FMQ concept
  - PT Anaemia Neonatal in FMQ Anemia
- PTs that specify an etiology for the FMQ concept
  - PT Uremic Pruritus in FMQ Pruritus
- PTs that ensure the occurrence of the FMQ concept
  - PT Aortic Rupture in FMQ Hemorrhage

FMQ Ground Rules: Broad Queries

Broad Queries: Reasonably suggestive of FMQ concept occurrence

- PTs that may result in the FMQ concept
  - PT Osteopenia in FMQ Osteoporosis
- PTs that provide laboratory, radiologic, or other diagnostic test results reasonably suggestive of an FMQ, including PTs with ambiguous results such as “abnormal”
  - PT Blood Glucose Abnormal in FMQ Hyperglycemia
- PTs reasonably suggestive of the FMQ concept, but not required by the FMQ concept:
  - PT Bronchospasm in FMQ Hypersensitivity
- PTs that indicate a “carrier” status for FMQ concepts that specify an infectious disease
  - PT Bacterial Disease Carrier in FMQ Bacterial Infection

FMQ Ground Rules: PT's Excluded from FMQ

PTs Excluded from FMQs: terms that are too vague

- PTs that are neither a required component nor reasonably specific for the FMQ concept
  - PT Nausea would not be included in FMQ Migraine
- PTs that provide the names of laboratory, radiologic, or other diagnostic tests without a result
  - PT Clostridium Test
  - PTs that provide test names without a result, but that would only be performed in the presence of disease, should be included if they otherwise qualify (example: PT Antipsychotic Drug Level in FMQ Psychosis).

How FMQs were Constructed

- FDA review staff developed standard groupings of related AEs.
- Each FMQ represents a distinct medical concept (e.g., Anemia, Nausea, Vomiting, etc.) and stand on their own.
- Each preferred term was independently adjudicated by a subject matter expert reviewer; any discrepancies were adjudicated by the working group.
- FMQ "Ground Rules" were created and used to apply medical judgment in developing logical groupings
- Steering committee made final decisions when there were difference of opinions; ensured version control, systems development, up-versioning with each major MedDRA release, and change control
- Cumulative approach: includes current PTs, former PTs, misspelled terms.

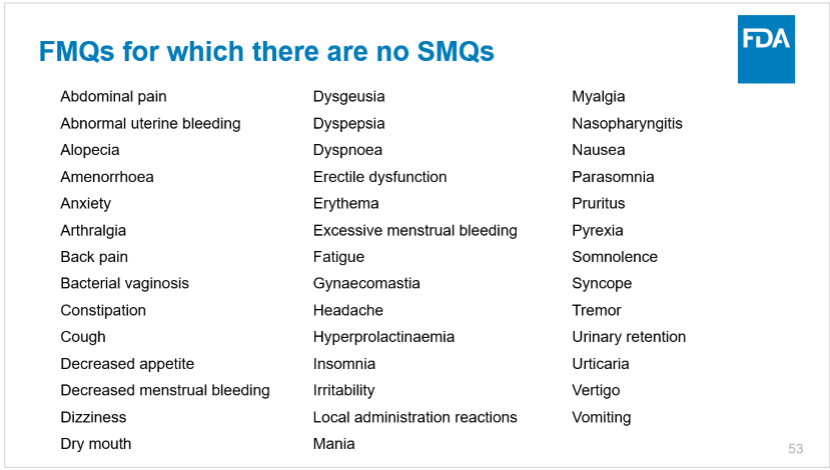
Difference Between FMQs and SMQs

FMQs attempt to capture all instances of an AE, even if PT indicates a “non” drug-related cause:

FMQ Pancreatitis **SMQ Acute Pancreatitis**

(Does Contain) **(Does Not Contain)**

Alcoholic Pancreatitis
Autoimmune Pancreatitis
Obstructive Pancreatitis
Pancreatitis Viral



FMQs for which there are no SMQs

Abdominal pain	Dysgeusia	Myalgia
Abnormal uterine bleeding	Dyspepsia	Nasopharyngitis
Alopecia	Dyspnoea	Nausea
Amenorrhoea	Erectile dysfunction	Parasomnia
Anxiety	Erythema	Pruritus
Arthralgia	Excessive menstrual bleeding	Pyrexia
Back pain	Fatigue	Somnolence
Bacterial vaginosis	Gynaecomastia	Syncope
Constipation	Headache	Tremor
Cough	Hyperprolactinaemia	Urinary retention
Decreased appetite	Insomnia	Urticaria
Decreased menstrual bleeding	Irritability	Vertigo
Dizziness	Local administration reactions	Vomiting
Dry mouth	Mania	

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FMQ version 2.1

1. Arthritis
2. Abdominal Pain
3. Abnormal Uterine Bleeding
4. Acute Coronary Syndrome
5. Acute Kidney Injury
6. Alopecia
7. Amenorrhea
8. Anemia
9. Anaphylactic Reaction
10. Angioedema
11. Anxiety
12. Arrhythmia
13. Arthralgia
14. Back Pain
15. Bacterial Infection
16. Bacterial Vaginosis
17. Bronchospasm
18. Cachexia
19. Cardiac Conduction Disturbance
20. Cholecystitis
21. Confusional State
22. Constipation
23. Cough
24. Decreased Appetite
25. Decreased Menstrual Bleeding
26. Depression
27. Diabetic Ketoacidosis
28. Diarrhea
29. Dizziness
30. Dry Mouth
31. Dysgeusia
32. Dyspepsia
33. Dyspnoea
34. Erectile Dysfunction
35. Erythema
36. Excessive Menstrual Bleeding
37. Fall
38. Fatigue
39. Fracture
40. Fungal Infection
41. Glaucoma
42. Gout
43. Gynaecomastia
44. Hemorrhage
45. Headache
46. Heart Failure
47. Hepatic Failure
48. Hepatic Injury
49. Hyperglycemia
50. Hyperprolactinaemia
51. Hypersensitivity
52. Hypoglycemia
53. Hypotension
54. Insomnia
55. Irritability
56. Invest Agent Abuse Potential
57. Leukopenia
58. Lipid Disorder
59. Local Administration Reactions
60. Malignancy
61. Mania
62. Myalgia
63. Myocardial Infarction
64. Myocardial Ischemia
65. Nasopharyngitis
66. Nausea
67. Opportunistic Infection
68. Osteoporosis
69. Palpitations
70. Pancreatitis
71. Paraesthesia
72. Parasomnia
73. Peripheral Oedema
74. Pneumonia
75. Pneumonitis
76. Pruritus
77. Psychosis
78. Purulent Material
79. Pyrexia
80. Rash
81. Renal & Urinary Tract Infection
82. Respiratory Depression
83. Respiratory Failure
84. Rhabdomyolysis
85. Seizure
86. Self-Harm
87. Sexual Dysfunction
88. Somnolence
89. Stroke-TIA
90. Syncope
91. Systemic Hypertension
92. Tachycardia
93. Tendinopathy
94. Thrombocytopenia
95. Thrombosis
96. Thrombosis (Arterial)
97. Thrombosis (Venous)
98. Tremor
99. Urinary Retention
100. Urticaria
101. Vertigo
102. Viral Infection
103. Volume Depletion
104. Vomiting

https://www.regulations.gov/docket/FDA-2022-N-1961/document

Algorithmic FDA Medical Queries

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FMQ Components

- **Narrow** – contains PTs highly specific to the FMQ concept; indicates that the FMQ occurred.

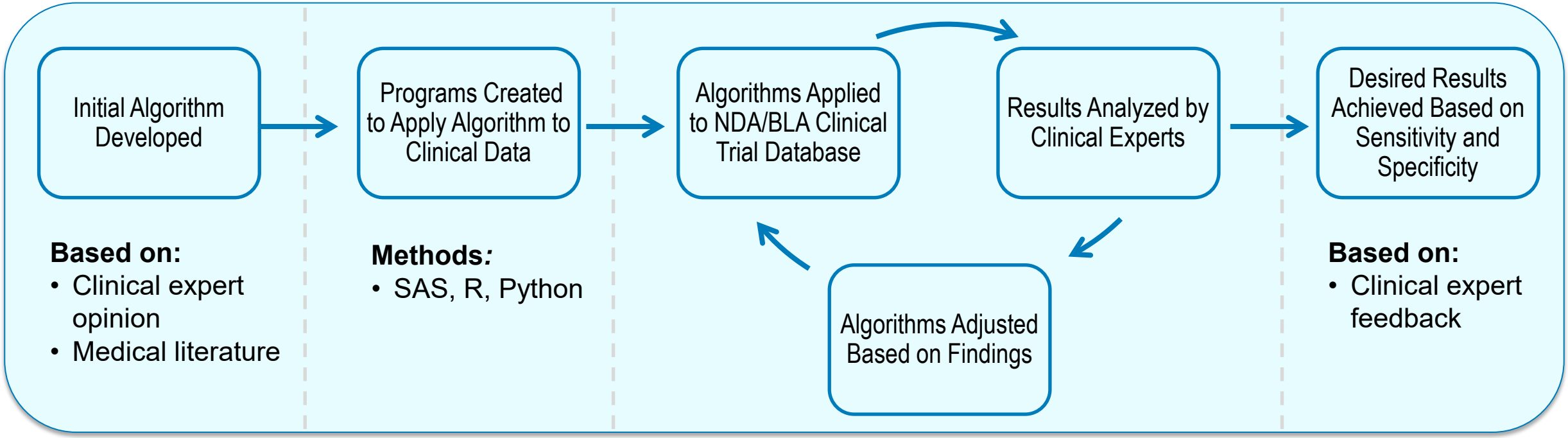
- **Broad** – casts a wider net to capture additional cases of the FMQ concept.

- **Algorithmic** – an important step forward because multiple datasets are combined to leverage the available information, such as:
  - Adverse event datasets
  - Laboratory datasets
  - Concomitant meds datasets
  - Medical history datasets
  - Temporal relationships

Example Mock Algorithm:

1. PT + PT
2. Lab value >ULN
3. PT + Con Med within 3 days
4. PT + Medical History

FMQ Algorithm Development and Testing Process



Based on:
- Clinical expert opinion
- Medical literature

Methods:
- SAS, R, Python

- Trial database of over 10,000 studies
- Algorithm applied multiple ways:
  - *Large random trial selection*
  - *Targeted trials with known FMQ associations*
  - *Trials with high prevalence of FMQ terms*
- Revised algorithm based on:
  - *Total patients and safety signals identified*
  - *Individual case reports and data*

Based on:
- Clinical expert feedback

Rhabdomyolysis Algorithmic FMQ

Patients qualify for the algorithm if they meet any of the following criteria:

1. Any Rhabdomyolysis FMQ Narrow term
2. Urine myoglobin >ULN
3. CPK >5 x ULN **AND NO:**
   - CPK >ULN at baseline OR
   - CPK-MB/CPK >0.05 with start date within 3 days
4. [PT Myalgia + PT Muscular Weakness + (PT Myoglobin Urine Present OR PT Chromaturia)] with start date within 7 days of each other

ULN= Upper limit of normal, CPK = creatine phosphokinase

Hypoglycemia Algorithmic FMQ

Patients qualify for the algorithm if they meet any of the following criteria:

1. Any Hypoglycemia FMQ Narrow Term
2. Plasma Glucose <54 mg/dL
3. [Any Hypoglycemia FMQ Broad Term* OR Supplemental Term**] PLUS [Plasma Glucose <70 mg/dL] with start date within 1 week
4. [≥2 Occurrences of a Hypoglycemia FMQ Broad Term* OR Supplemental Term**] PLUS [≥2 Occurrences of Plasma Glucose <70 mg/dL]

* Includes Hypoglycemia FMQ Broad Terms only (while FMQ Broad analyses include both Narrow and Broad terms, this criterion only refers to the terms specifically identified as Broad).

** Supplemental Terms – Accident, Anxiety, Asthenia, Cold sweat, Coma, Confusional state, Fall, Fatigue, Hunger, Hyperhidrosis, Irritability, Loss of consciousness, Palpitations, Road traffic accident, Seizure, Tremor, Dysarthria, Balance disorder, Coordination abnormal, Headache, Vision blurred, and Visual impairment.

Hyperglycemia Algorithmic FMQ

Patients qualify for the algorithm if they meet any of the following criteria:

1. Any PT from Hyperglycemia FMQ Narrow
2. Fasting Plasma Glucose ≥126 mg/dL
3. ≥2 Plasma Glucoses >180 mg/dL
4. Any New Diabetes Concomitant Medication:
   - The medication must have been started following enrollment
   - CMINDC File
     - INCLUDE diab, mellitus, hyperglyc, glucose, dibet, dieb
     - EXCLUDE prophyla, prevent, insipidus, hyperglycerid, low blood glucose, low glucose, low blood sugar, low sugar, low afternoon blood glucose, low morning blood glucose
   - CMCLAS File
     - INCLUDE gliptin, glutide, diabet, glitaz, glucose lowering, glucosidas, dipeptidyl, sulfonyl, DPP, guanide, GLP, glucagon-like, metform, gliflozin, insulin, sodium-glucose, SGLT, thiazolid
     - EXCLUDE sex hormone
5. Post Baseline HbA1c ≥6.5%
6. HbA1c Increase ≥0.3% with Post Baseline HbA1c ≥5.7%
7. Change from Baseline Fasting Plasma Glucose ≥20 mg/dL with Post Baseline FPG >100 mg/dL

Hypersensitivity Algorithmic FMQ

A patient is included in the algorithm by having items from any of the following categories or combinations of categories with start dates within 7 days:

1. Category A
2. Category B + Category C
3. Category B + Category D
4. Category C + Category D

Category A (Narrow PTs)	Category B (Respiratory)	Category C (Skin)	Category D (Systemic Reactions)
Acute generalised exanthematous pustulosis	Allergic bronchitis	Administration related reaction	Acute circulatory failure
Administration site hypersensitivity	Allergic pharyngitis	Administration site dermatitis	Blood immunoglobulin E abnormal
Administration site recall reaction	Allergic respiratory symptom	Administration site pruritus	Blood pressure decreased
Administration site vasculitis	Asthma	Administration site rash	Blood pressure diastolic decreased
Allergic colitis...	Asthmatic crisis...	Administration site urticaria...	Blood pressure systolic decreased...

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Including Grouped Term Information in the ADVERSE REACTIONS Section of the Prescribing Information

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Disclaimer

- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to illustrate concepts/challenges and should not be considered FDA recommended templates.

Overview of Presentation

- Discuss considerations on including group term (e.g., FMQ) information and component term information in the ADVERSE REACTIONS section of labeling

- Discuss updated prescription drug labeling resources

FMQs = FDA Medical Queries

Adverse Events vs. Adverse Reactions in Labeling

- **Adverse Events** (AEs): "Any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related"[1]

- **Adverse Reactions** (ARs): "An undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all AEs observed during use of a drug, only those AEs for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the AE."[2]

[1] See guidance for industry: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (January 2006) (referred to as the Adverse Reactions Section of Labeling Guidance)

[2] For PLR-formatted labeling, see 21 CFR 201.57(c)(7) and the Adverse Reactions Section of Labeling Guidance. For "old" (non-PLR) format labeling, the AR definition is different [21 CFR 201.80(g)]: *"an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."*

Factors in Causality Assessment of AEs[1]

(helps determine if an AE is an AR and is appropriate for inclusion in the labeling)

- Increased frequency of reporting
- AE rate for the drug exceeds the placebo rate
- Dose-response relationship
- AE is consistent with the pharmacology of the drug
- Relationship between time of AE relative to the time of drug exposure
- Challenge and dechallenge cases
- AE is known to be caused by related drugs
- AE observed across studies
- AE led to higher discontinuation rate or serious adverse reactions in the drug-treated group

[1] AE = adverse event; AR = adverse reactions; See Adverse Reactions Section of Labeling Guidance

Including Group Term Information into *Clinical Trials Experience* Subsection of ADVERSE REACTIONS Section

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 DRUG ABUSE AND DEPENDENCE
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Common Adverse Reaction Table(s)

Example of Common Adverse Reaction Table[1,2] in the *Clinical Trials Experience* Subsection of ADVERSE REACTIONS Section

Table X: Common Adverse Reactions in Patients with Disease-X During the 24-week Treatment Period in Studies A, B, and C[1]		
	DRUG-X N=XXX	Placebo N=XXX
Asthenia[2]	39%	17%
Musculoskeletal pain[3]	18%	7%
Vomiting	15%	11%
Upper respiratory tract infection	12%	3%
Thrombocytopenia	9%	2%
Anemia	9%	3%
Arthralgia	6%	3%
Headache	6%	4%
Herpes Zoster	5%	2%
Paresthesia	5%	3%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients

[2] Asthenia includes the terms fatigue and malaise

[3] Musculoskeletal pain includes back pain, neck pain, thigh pain, shoulder pain

[1] The *Clinical Trials Experience* subsection of the ADVERSE REACTIONS section "must list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database" – see 21 CFR 201.57(c)(7)(ii)(A)

[2] "To permit side-by-side comparison of adverse reaction rates, common adverse reactions are typically presented in a table" – see Adverse Reactions Section of Labeling Guidance

Merits of Grouping Related Terms

- Include an AR that was not initially apparent when reporting was spread across multiple related individual terms
- Provide a better estimate of the true magnitude of the AR; and
- Exclude an AE that is unrelated or unlikely related to the drug when analysis of grouped terms does not support determination that the AE is an AR

ARs = adverse reactions; AEs = adverse events

Classifying Adverse Reactions in the *Clinical Trials Experience Subsection* in the ADVERSE REACTIONS Section[1]

- AR that represent same phenomenon should ordinarily be grouped together as a single AR to avoid diluting or obscuring the true effect

- AR reported in more than one body system that appear to represent a common pathophysiologic AR should be grouped together to better characterize the AR

AR = adverse reactions; [1] See Adverse Reactions Section of Labeling Guidance.

Four Fictitious Labeling Examples

#1 Data Only Supports Including Anxiety FMQ Term (in Common AR Table in ADVERSE REACTIONS section)

FMQ Anxiety Analysis (this does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety Grouped Term	**6.7%**	**2.7%**
Anxiety	3.3%	1.3%
Anxiety aggravated	1.5%	0.8%
Anxiety disorder	1.5%	0.7%
Anxiety disorder NEC	0.8%	0.1%

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]		
	DRUG-X N=XXX	Placebo N=XXX
Vomiting	10%	2%
Diarrhea	9%	3%
Dermatitis	8%	3%
Anxiety[2]	7%	3%
Chills	5%	3%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients
2 Anxiety is composed of several similar terms

1. **FMQ Anxiety Grouped Term is an AR (included in table body)**
2. **Component terms represented in common AR table; however, they are not named because they are near-synonyms.**
3. **Footnote states that grouped term includes other related terms.**

#2 Include FMQ Grouped Term in Body of Table and Component Term(s) in Footnotes in Most Common AR Table in ADVERSE REACTIONS Section

FMQ Anxiety Analysis (this does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety	**12.2%**	**2.2%**
Social phobia	5.1%	2.1%
Stress	2.1%	0.1%
Anxiety disorder	2.5%	0%
Anxiety disorder NEC	2.1%	0%
Anxiety	2.1%	0%

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]

	DRUG-X N=XXX	Placebo N=XXX
Anxiety[2]	12%	2%
Vomiting	10%	2%
Diarrhea	9%	3%
Dermatitis	8%	3%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients

[2] Anxiety includes social phobia and stress and other related reactions

1. **FMQ Anxiety Grouped Term is an AR (included in table body)**
2. **Social phobia and stress included in grouped term and named in footnote because distinct clinical events and not near-synonyms**

#3.1 Include FMQ Grouped Term and Clinically Important Component Term(s) in Footnotes in Most Common AR Table in ADVERSE REACTIONS Section

FMQ Anxiety Analysis (this does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety	**9.2%**	**2.2%**
Panic disorder	4.1%	2.1%
OCD	2.1%	0.1%
Anxiety disorder	1.4%	0%
Anxiety disorder NEC	1.3%	0%
Anxiety	1.2%	0%

OCD = obsessive compulsive disorder

Components in footnotes

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]		
	DRUG-X N=XXX	Placebo N=XXX
Vomiting	10%	2%
Anxiety[2]	9%	2%
Dermatitis	8%	3%
Adverse reaction-a	x%	x%
Adverse reaction-b	x%	x%
Adverse reaction-c	x%	x%
Adverse reaction-d	x%	x%
Adverse reaction-e	x%	x%
Adverse reaction-f	x%	x%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients

[2] Anxiety includes panic disorder and obsessive compulsive disorder and other related reactions

1. **FMQ Anxiety Grouped Term is an AR (included in table body)**
2. **Panic disorder and OCD included in grouped term and in footnotes**

#3.2 Include FMQ Grouped Term and Clinically Important Component Term(s) in Body of Table in Most Common AR Table in ADVERSE REACTIONS Section

FMQ Anxiety Analysis (this does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety	**9.2%**	**2.2%**
Panic disorder	4.1%	2.1%
OCD	2.1%	0.1%
Anxiety disorder	1.4%	0%
Anxiety disorder NEC	1.3%	0%
Anxiety	1.2%	0%

OCD = obsessive compulsive disorder

Components in body of table

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]		
	DRUG-X N=XXX	Placebo N=XXX
Vomiting	10%	2%
Anxiety[2]	9%	2%
Panic disorder	4%	2%
Obsessive compulsive disorder	2%	< 1%
Dermatitis	8%	3%

[1] Adverse reactions that occurred in ≥ 5% in DRUG-X-treated patients and ≥ 2% than placebo-treated patients
[2] In addition to panic disorder and obsessive compulsive disorder, anxiety includes other related reactions

1. **FMQ Anxiety Grouped Term is an AR (included in table body)**
2. **Panic disorder and OCD included in grouped term and in table body because distinct clinical events and clinical importance**

#4 Data Only Supports Including ≥ 1 FMQ Component(s) in Common AR Table in ADVERSE REACTIONS Section

FMQ Anxiety Analysis (this table does not go into labeling)		
	DRUG-X N=XXX	Placebo N=XXX
FMQ Anxiety	**11.1%**	**2.7%**
Panic disorder	5.2%	0.4%
OCD	4.6%	0.1%
Nervousness	1.1%	0.9%
Anxiety disorder NEC	0.3%	0.1%
Anxiety aggravated	0.2%	0.2%
Anxiety postoperative	0%	1%

OCD = obsessive compulsive disorder

Table X: Common Adverse Reactions in Patients with Disease-X (48-week Studies 1 and 2)[1]		
	DRUG-X N=XXX	Placebo N=XXX
Vomiting	10%	2%
Diarrhea	9%	3%
Dermatitis	8%	3%
Panic disorder	5%	<1%
OCD	5%	<1%
[1] AR that occurred in ≥ 5% in DRUG-X treated patients and ≥ 2% than placebo-treated patients		

1. **Only panic disorder and OCD component terms meet AR definition and only apparent drivers of signal**
2. **Anxiety grouped term not included in table**

Summary of the FMQ Labeling Paradigm[1] (1 of 2)

1. FMQ grouped term(s) are included in common AR table if they meet the regulatory definition of an AR

2. If a grouped term and component term(s) meet the definition of an AR but the component term(s) are the only apparent driver(s) of the signal, only those component term(s) will be included in the body of the common AR table

[1] Labeling paradigm for your consideration applies to the common adverse reactions table(s) in the *Clinical Trials Experience* subsection in the ADVERSE REACTIONS section

Summary of the FMQ Labeling Paradigm[1] (2 of 2)

3. Component terms that contribute to a grouped term are represented in the common AR table by being part of the group term incidence.

If the component terms are:

- Near synonyms of the grouped term, they are not mentioned in the body or footnotes in the table
  - Footnote will state that the grouped term includes related terms
- Distinct clinical events and not near synonyms of grouped term, they are mentioned in footnotes OR in the body of the table.

[1] Labeling paradigm for your consideration applies to the common adverse reactions table(s) in the *Clinical Trials Experience* subsection in the ADVERSE REACTIONS section

FDA's Labeling Resources for Human Prescription Drugs

FDA's Labeling Resources for Human Prescription Drugs

For Industry

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FDA's labeling resources for human prescription drugs are primarily directed to industry staff who develop human prescription drug* labeling. Human prescription drug labeling (1) contains a summary of the essential scientific information needed for the safe and effective use of the drug; and (2) includes the Prescribing Information, FDA-approved patient labeling (Medication Guides, Patient Package Inserts, and/or Instructions for Use), and/or carton and container labeling.

If you are a healthcare professional, patient, or caregiver, visit Frequently Asked Questions about Labeling for Prescription Medicines.

- **Searchable Labeling Databases**
- **How May "Current" Labeling Be Different Than "FDA-Approved" Labeling**
- **Searchable Product Databases**
- **Imported-Drug Specific Labeling Resources**
- **Resources for Promotional Labeling and Other FDA-Regulated Products**

[1] FDA's Labeling Resources for Human Prescription Drugs webpage available at https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

Prescribing Information Resources

for Industry

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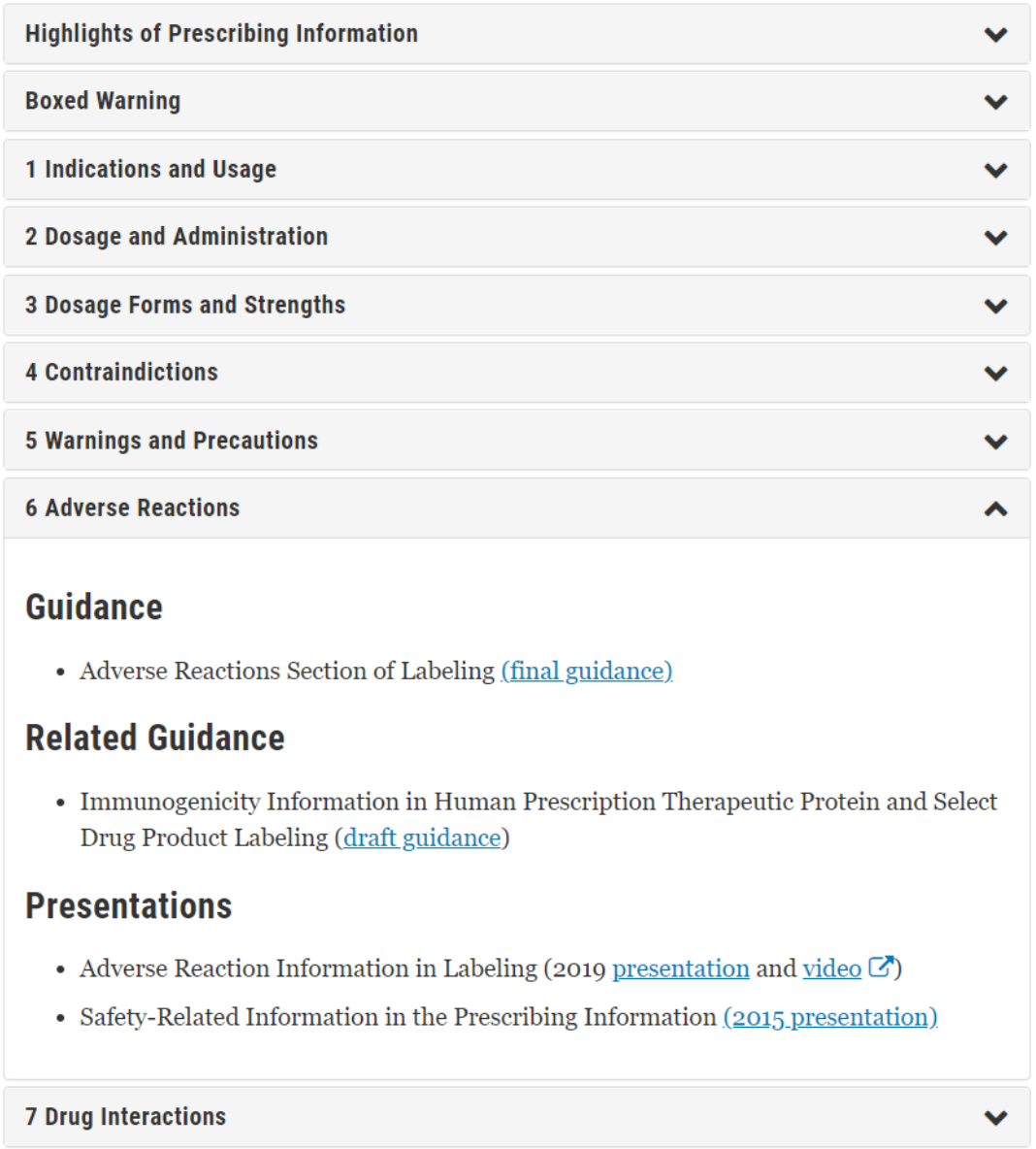
- **Highlights of Prescribing Information**
- **Boxed Warning**
- **1 Indications and Usage**
- **2 Dosage and Administration**
- **3 Dosage Forms and Strengths**
- **4 Contraindictions**
- **5 Warnings and Precautions**
- **6 Adverse Reactions**
- **7 Drug Interactions**

[1] Prescribing Information Resources webpage available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

Prescribing Information Resources



[1] Prescribing Information Resources webpage available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

Frequently Asked Questions about Labeling for Prescription Medicines

For Healthcare Professionals and Patients

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Frequently asked questions about labeling for prescription drugs (medicines) on this webpage are primarily directed to healthcare professionals (for example, doctors, nurse practitioners, physician assistants, pharmacists, nurses) and patients and their caregivers. For information about prescription drug labeling resources primarily directed to industry such as those for the Prescribing Information, FDA-approved patient labeling, carton and container labeling, biological product labeling, generic drug labeling, labeling databases, and product databases visit FDA's Labeling Resources for Prescription Drugs.

Labeling for prescription medicines is FDA's primary tool for communicating drug information to healthcare professionals, and patients and their caregivers. Labeling for prescription medicines includes:

- Prescribing Information (labeling for healthcare professionals),
- Carton and container labeling (cartons and containers are outside packaging that contain information about prescription medicines), and
- Labeling for patients or caregivers (e.g., Medication Guides, Patient Package Inserts,

[1] FAQs about Labeling for Prescription Medications is available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/frequently-asked-questions-about-labeling-prescription-medicines

Discussion

What questions or comments do you have about the FDA Medical Queries?

Contact us at ONDbiomedicalinformatics@fda.hhs.gov


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ADMINISTRATION

BACK-UP SLIDES

Grouping Strategy for FMQs vs. MedDRA Hierarchy

MedDRA Hierarchy

- Combines PTs using multiple strategies – anatomy, pathology, physiology, etiology, manifestation site, purpose, and function
- Groups AE and non-AE PTs – such as therapeutic indications, investigations, product quality issues, medical procedures, and medical/social family history characteristics

FMQs

- Grouping strategy more focused – only goal is to create clinically meaningful groupings
- Only groups AE PTs

Example: Abdominal Pain FMQ

Abdominal discomfort	Narrow
Abdominal migraine	Narrow
Abdominal pain	Narrow
Abdominal pain aggravated	Narrow
Abdominal pain lower	Narrow
Abdominal pain NOS	Narrow
Abdominal pain upper	Narrow
Abdominal rebound tenderness	Narrow
Abdominal rigidity	Narrow
Abdominal tenderness	Narrow
Acute abdomen	Narrow
Enteric neuropathy	Narrow
Epigastric discomfort	Narrow
Gastrointestinal discomfort	Narrow
Gastrointestinal pain	Narrow
Gastrointestinal pain NOS	Narrow
Gastrointestinal upset	Narrow
Intestinal spasm	Narrow
Perihepatic discomfort	Narrow
Spleen pain	Narrow
Stomach discomfort	Narrow
Ulcer type pain	Narrow
Carnett's sign positive	Broad
Complicated appendicitis	Broad
Gastric irritation	Broad
Helicobacter duodenal ulcer	Broad
Infantile colic	Broad
Large intestine infection	Broad
Ulcerative duodenitis	Broad
Visceral pain	Broad

HLT Gastrointestinal and abdominal pains (excl oral and throat)

- **Abdominal migraine**
- **Abdominal pain**
- **Abdominal pain lower**
- **Abdominal pain upper**
- **Abdominal rebound tenderness**
- **Abdominal rigidity**
- **Abdominal tenderness**
- **Gastrointestinal pain**
- **Infantile colic**
- Oesophageal pain
- **Visceral pain**

HLT Gastrointestinal signs and symptoms NEC

- **Abdominal discomfort**
- Abdominal symptom
- **Acute abdomen**
- Anal incontinence
- Bradyphagia
- Breath odour
- Bruxism
- Cullen's sign
- Dumping syndrome
- Dysphagia
- Dysphagia lusoria
- Early satiety
- Encopresis
- Fixed bowel loop
- Foetor hepaticus
- Gastrocardiac syndrome
- Gastrointestinal somatic symptom disorder
- Gastrointestinal wall thickening
- Gastrointestinal wall thinning
- Hiccups
- Hyperphagia
- Hypophagia
- Incontinence
- Intestinal calcification
- Intestinal congestion
- Malignant dysphagia
- Mastication disorder
- Merycism
- Myochosis
- Oesophageal discomfort
- Oesophageal food impaction
- Pelvic discomfort
- Pelvic pain
- Peripancreatic fluid collection
- Peristalsis visible
- Pharyngeal dystonia
- Portal venous gas
- Post cholecystectomy syndrome
- Radiation dysphagia
- Radiation sickness syndrome
- White nipple sign
- Wischnewsky spots

Differences between FMQs and SMQs

SMQs use multiple strategies for grouping whereas FMQs focus on premarket assessment

FMQ specificity:

SMQ Acute Central Respiratory Depression **CONTAINS** *Breath sounds abnormal*

↓

FMQ Respiratory Depression **OMITS** *Breath sounds abnormal*

FMQ sensitivity:

FMQ Pancreatitis **CONTAINS** *Cytomegalovirus pancreatitis* **AND** *Pancreatitis mumps*

↓

SMQ Acute Pancreatitis **DOES NOT CONTAIN** *Cytomegalovirus pancreatitis* **OR** *Pancreatitis* mumps

FMQs for which there are no SMQs

Abdominal pain
Abnormal uterine bleeding
Alopecia
Amenorrhoea
Anxiety
Arthralgia
Back pain
Bacterial vaginosis
Constipation
Cough
Decreased appetite
Decreased menstrual bleeding
Dizziness
Dry mouth
Dysgeusia
Dyspepsia
Dyspnoea
Erectile dysfunction
Erythema
Excessive menstrual bleeding
Fatigue
Gynaecomastia
Headache
Hyperprolactinaemia
Insomnia
Irritability
Local administration reactions
Mania
Myalgia
Nasopharyngitis
Nausea
Parasomnia
Pruritus
Pyrexia
Somnolence
Syncope
Tremor
Urinary retention
Urticaria
Vertigo
Vomiting