Teratogenic Risk Impact Mitigation (TRIM): Development of explicit criteria to facilitate decisions regarding teratogenic risk mitigation strategies

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eTable 1. Summary of current REMS targeting teratogenic effects

Drug Name	Indication	Drug approval date	REMS approval date
Bosentan	Pulmonary Hypertension	11/20/2001	3/25/2008
Ambrisentan	Pulmonary Hypertension	6/15/2007	5/29/2009
Thalidomide	Multiple myeloma	7/16/1998	8/3/2010
Lenalidomide	Transfusion-dependent anemia due to myelodysplastic syndromes	12/27/2005	8/3/2010
Isotretinoin	Severe recalcitrant nodular acne	5/7/1982	10/22/2010
Phentermine/ topiramate	Chronic weight management	7/17/2012	7/17/2012
Mycophenolate	Prophylaxis of organ rejection	5/3/1995	9/25/2012
Pomalidomide	Multiple myeloma	2/8/2013	2/8/2013
Riociguat	Pulmonary Hypertension	10/8/2013	10/8/2013
Macitentan	Pulmonary Hypertension	10/18/2013	10/18/2013
Spartentan	Primary IgA Nephropathy	2/17/2023	2/17/2023

Source: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

eTable 2. TRIM Criteria Development Expert Panel

	Sex	Area of Expertise	Sector	Prior experience with risk mitigation decision making	Experience caring for pregnant patients	Attendance in Focus Group (n=29)	Delphi Rounds	
							Round 1 (n=30)	Round 2 (n=28)
1	F	Obstetrics and Gynecology	Academia/Clinical Practice	No	Yes	✓	✓	✓
2	M	Perinatal Epidemiology	Academia/ Clinical Practice	Yes	Yes	-	✓	✓
3	F	Perinatal Epidemiology	Academia	Yes	No	✓	✓	✓
4	F	Pediatrics, Obstetrics and Gynecology	Academia	Yes	No	-	✓	✓
5	F	Family Medicine	Academia/ Clinical Practice	Yes	Yes	✓	✓	✓
6	F	Clinical Genetics	Academia/ Clinical Practice	No	Yes	✓	✓	✓
7	M	Obstetrics and Gynecology	Academia/ Clinical Practice	Yes	Yes	✓	✓	✓
8	F	Perinatal Epidemiology	Academia	Yes	Yes	✓	✓	✓
9	F	Obstetrics and Gynecology	Academia/ Clinical Practice	Yes	Yes	✓	✓	✓
10	F	Obstetrics and Gynecology	Academia/ Clinical Practice	No	Yes	✓	✓	✓
11	M	Internal Medicine	Academia/ Clinical Practice	Yes	No	✓	-	-
12	F	Obstetrics and Gynecology	Academia/ Clinical Practice	No	Yes	✓	✓	✓
13	F	Obstetrics and Gynecology	Academia	No	No	✓	✓	✓
14	F	Obstetrics and Gynecology, Psychiatry	Academia/ Clinical Practice	No	Yes	✓	✓	✓
15	M	Obstetrics and Gynecology/ Teratology	Academia/ Clinical Practice	No	Yes	✓	✓	✓
16	F	Obstetrics and Gynecology	Academia/ Clinical Practice	No	Yes	✓	✓	✓
17	F	Obstetrics and Gynecology, Genetics and Genome Sciences	Academia/ Clinical Practice	No	Yes	✓	✓	✓

18	F	Psychiatry and Behavioural Sciences, Obstetrics and Gynecology	Academia/ Clinical Practice	Yes	Yes	✓	✓	✓
19	M	Internal Medicine	Academia/ Clinical Practice	Yes	No	✓	-	-
20	F	Gastroenterology, Hepatology and Nutrition	Academia/ Clinical Practice	No	Yes	✓	✓	-
21	F	Reproductive toxicology, Teratology	Pharmaceutical Industry	Yes	No	✓	✓	✓
22	M	Reproductive toxicology, Teratology	Pharmaceutical Industry	No	No	✓	✓	✓
23	F	Pharmacoepidemiology	Pharmaceutical Industry	Yes	No	✓	✓	✓
24	M	Risk Management and Pharmacovigilance	Pharmaceutical Industry	Yes	No	✓	✓	✓
25	M	Pharmacoepidemiology	Pharmaceutical Industry	Yes	No	✓	✓	✓
26	F	Pregnancy, Reproductive toxicology	Pharmaceutical Industry	Yes	No	✓	✓	✓
27	F	Pharmacoepidemiology	Pharmaceutical Industry	Yes	No	✓	✓	✓
28	F	Pregnancy and Reproductive toxicology	Pharmaceutical Industry	Yes	No	✓	✓	✓
29	F	Risk Management and Pharmacovigilance	Pharmaceutical Industry	Yes	No	✓	✓	✓
30	F	Pharmacoepidemiology	Pharmaceutical Industry	Yes	No	✓	✓	✓
31	F	Risk Management and Pharmacovigilance	Pharmaceutical Industry	Yes	No	✓	✓	✓
32	F	Patient Advocate	Patient Advocacy	No	No	-	✓	-

eTable 3: Focus Group Discussion Questions

1. What are the critical factors in evaluating a teratogenic drug for advanced risk mitigation (e.g. REMS)?
2. What are your thoughts about the role of scientific evidence on teratogenic risk? (Moderator might suggest: animal data, human data, quality of evidence, the magnitude of risk, study designs, etc.)
3. What are your thoughts about the nature of adverse effects in humans? (Moderator might suggest: frequency, severity, and extent of the resultant disability)?
4. What are your thoughts about the drug characteristics? (Moderator might suggest: first-in-class, new molecular entity, route of administration, treatment duration, superior efficacy compared to alternatives)
5. What are your thoughts about the drug utilization data? (Moderator might suggest: small or large population, actual or market forecast)
6. What are your thoughts about disease-related factors? (Moderator might suggest: severity, treatment alternatives, the potential to harm fetus due to uncontrolled disease)
7. What are your thoughts about the target population at risk? (Moderator might suggest: size, social determinants of health, expected adherence to pregnancy prevention, pregnancy planning, off-label use)
8. What are your thoughts about the healthcare context? (Moderator might suggest: inpatient or outpatient use, prescriber specialty)
9. What are your thoughts about the regulatory context? (Moderator might suggest: precedents, previous experiences with REMS)
10. What are your thoughts about the anticipated impact of a risk mitigation programs on risk reduction and burden on the healthcare system?
11. Imagine you had a chance to require or retire a risk mitigation program for a teratogenic drug today. Why would you make that decision?

eTable 4. Questions posed to the panel members in Delphi round 1 & 2

Question 1: Do the above criteria sufficiently capture what you think needs to be considered when determining whether a medication needs risk mitigation?

Question 2: Are there any proposed criteria that do not meet your assessment of relevance? Would you consider removing one?

Question 3: It is critical for the development of TRIM to ensure that each criterion is distinct (i.e., does not have any overlap with other criteria). Please review the proposed list of criteria for distinctiveness in their scope. Are there any criteria which you think can be consolidated?

eTable 5. Criteria proposed during the focus group meeting

1. Access to contraception and abortion
2. Availability of alternative therapy
3. Safety and efficacy of alternatives
4. Clinical setting
5. Fetal dose ratio to cause teratogenic effect
6. High potential for dosing errors
7. Drug characteristic (half-life of elimination, uptake through placenta, impact of pharmacogenomic properties, narrow vs wide therapeutic window)
8. Drug interactions
9. Duration of exposure
10. Efficacy of the drug
11. Frequency of adverse event
12. Frequency of use during pregnancy
13. Known mechanism of teratogenicity (genotoxic vs fetotoxic)
14. Indication (life-threatening disease vs mild disease)
15. Interaction between disease and medication
16. Long term effects of adverse outcomes
17. Potential for misuse or inappropriate use (not taken as prescribed)
18. Off-label use
19. Potential sharing of medication
20. Prescriber specialty
21. Prevalence of condition being treated
22. Risk vs benefit of the medication- on fetus, pregnancy complications
23. Risk vs benefit of the medication- on neonate
24. Route of administration and risk for systemic absorption
25. Seriousness / Severity of adverse outcome
26. Chronicity of the adverse outcome (short term vs long term)
27. Strength of evidence - teratogenicity
28. Target population and risk for pregnancy
29. Timing of exposure during pregnancy
30. Time frame (during gestation) of teratogenicity
31. Certainty of risk
32. Unmet medical need
33. Unintended exposure (male partner taking teratogenic drug)