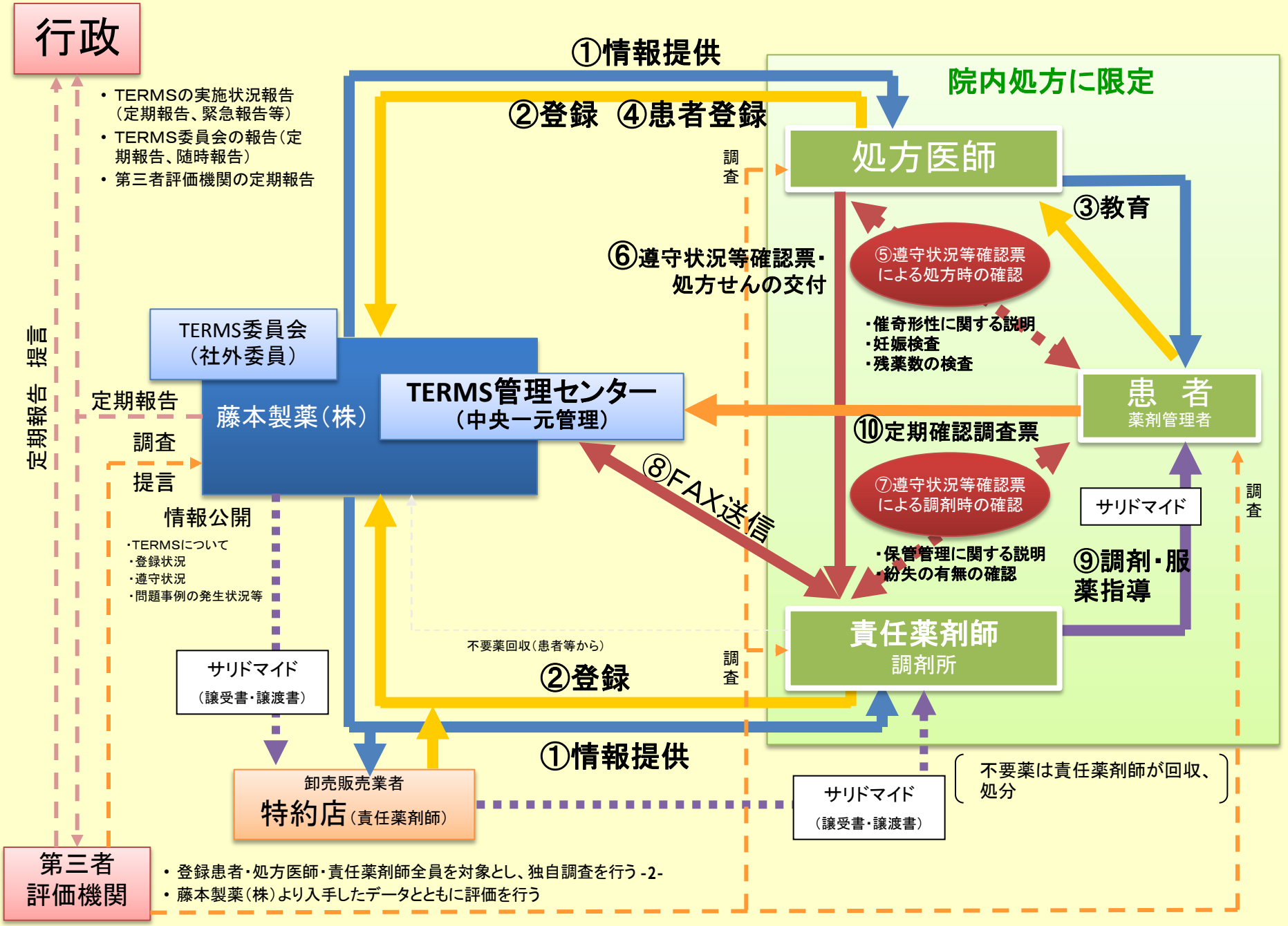
資料２

日米欧におけるサリドマイド安全管理システムの概要

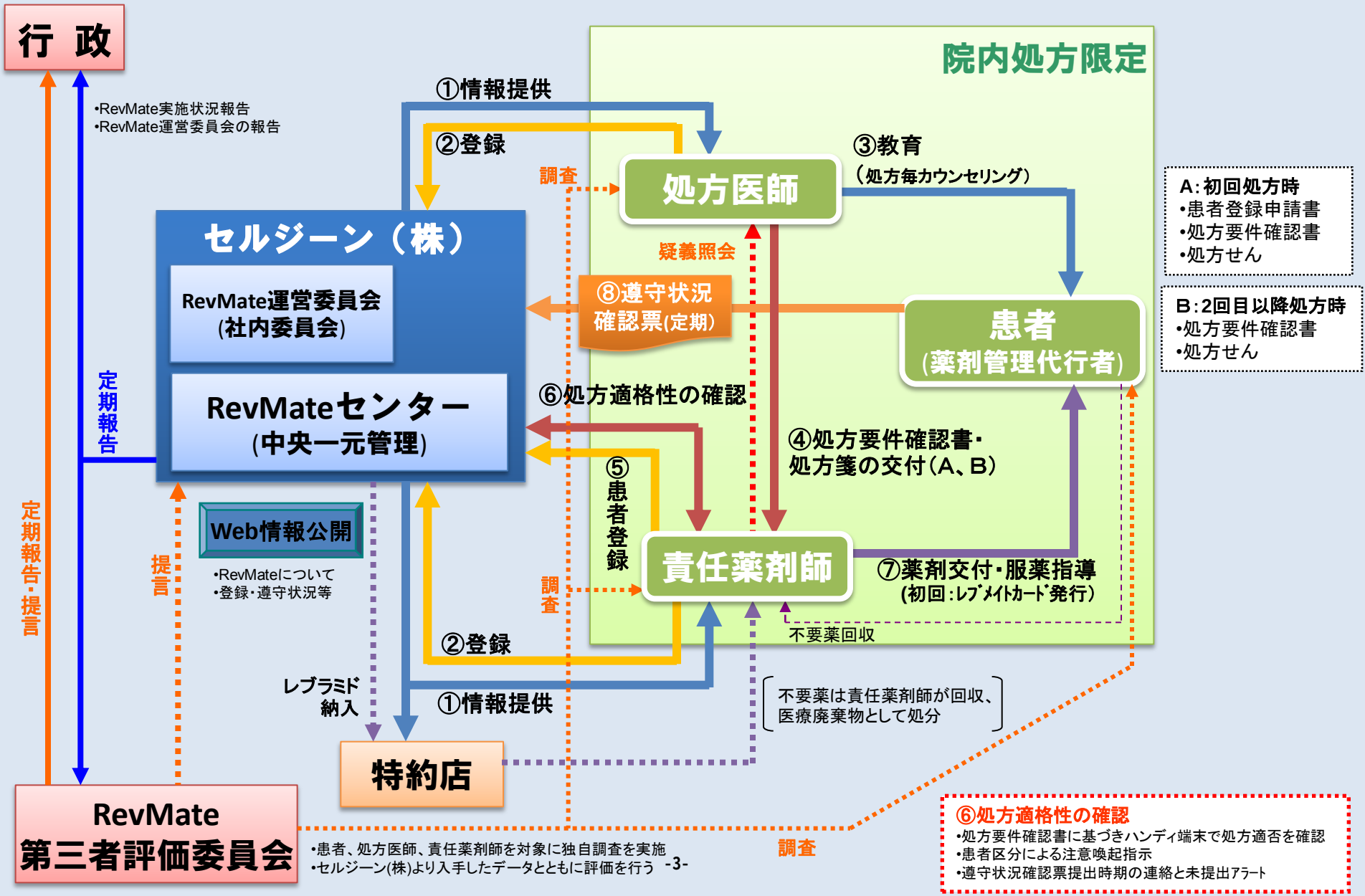
		日本		米国		欧州（EU-RMP）	ドイツ	イタリア
		TERMS（サリドマイド）	RevMate（レナリドミド）	STEPS（サリドマイド）	RevAssist（レナリドミド）			
基本事項	管理主体	藤本製薬株式会社	セルジーン株式会社	Celgene Corporation	Celgene Corporation	規制当局（各加盟国）	規制当局（BfArM）	規制当局（AIFA）
	院外処方	院内処方のみ	院内処方のみ	院外処方可	院外処方可	院外処方可	院外処方可	院内処方のみ
処方前	医師の教育	医師用冊子による	医療関係者向け冊子による	医師用冊子による	医師用冊子による	医療関係者向け冊子による	医療関係者向け冊子による	医療関係者向け冊子による
	医師の登録	企業に登録	企業に登録	企業に登録	企業に登録	×	規制当局に登録	規制当局に登録
	薬剤師（薬局）の教育	責任薬剤師冊子による	医療関係者向け冊子による	薬剤師冊子による	薬剤師冊子による	医療関係者向け冊子による	医療関係者向け冊子による	医療関係者向け冊子による
	薬剤師（薬局）の登録	責任薬剤師を企業に登録	責任薬剤師を企業に登録	薬局を企業に登録	薬局を企業に登録	×	×	×
	患者の教育	患者用冊子、避妊方法解説書、ＤＶＤ等	患者用冊子、避妊方法解説書、ＤＶＤ等	患者用冊子、避妊方法解説書等	患者用冊子、避妊方法解説書等	患者向け冊子、患者カード等	患者向け冊子、セラピーパス等	患者向け冊子等
	患者の登録	企業に登録 （氏名、住所、電話番号、生年月日等）	企業に登録 （氏名、生年月日）	企業に登録 （氏名、住所、電話番号、生年月日、社会保障番号等）	企業に登録 （氏名、住所、電話番号、生年月日、社会保障番号等）	×	×	規制当局に登録 （氏名（３文字）、生年月日、出生地、社会保障番号等）
	薬剤管理者の設置	○	○	×	×	×	×	×
２回目以降の処方時	医師からの説明の記録	遵守状況確認票 （妊娠回避、リスクについて説明、企業に登録）	処方要件確認書 （妊娠回避、リスクについて説明、企業に登録）	IVR※にて記録 （企業に登録）	IVR※にて記録 （企業に登録）	×	T-処方せんにてチェック	×
	妊娠検査（毎月）	○ 結果を企業に報告	○ 結果を企業に報告	○ 結果を企業に報告	○ 結果を企業に報告	△ 結果は記録のみ	△ 結果は記録のみ	○ 結果は規制当局に登録
	残薬数の確認	○	○	×	×	×	×	×
	薬剤師からの説明の記録	遵守状況確認票 （薬剤管理について説明、企業に登録）	×	×	×	×	×	×
	患者の理解度の確認	定期確認調査票にて実施 （直接企業に報告）	遵守状況確認票にて実施 （直接企業に報告）	IVR※にて実施 （直接企業に報告）	IVR※にて実施 （直接企業に報告）	×	×	×
その他	卸業者登録	○	×	× （セルジーン社から薬局に直送）	× （セルジーン社から薬局に直送）	×	×	×
	第三者機関による評価	○	○	○	○	×	×	×
	行政への報告	○ （３ヶ月毎に、登録状況、処方及び調剤状況、薬剤管理状況、曝露疑い発生状況、TERMS 委員会及び第三者評価期間の報告書等を報告）	○ （定期的に、遵守状況、第三者評価委員からの提言等について報告	○ （３ヶ月毎に、新規登録数、患者背景、遵守・逸脱状況、妊娠検査結果、STEPS に関する苦情等を報告）	○ （半年毎に、遵守状況等を報告）	○ （EMA へ半年毎に、妊娠防止プログラムの実施状況、推定使用量を報告）	○ （EMA へ半年毎に、妊娠防止プログラムの実施状況、推定使用量を報告）	○ （EMA へ半年毎に、妊娠防止プログラムの実施状況、推定使用量を報告）
	運用状況の公表	○	×	×	×	×	×	×
	不要薬の返却	医療機関に返却	医療機関に返却	セルジーン又は医療機関に返却	セルジーン又は医療機関に返却	薬剤師に返却	薬剤師に返却	薬剤師に返却
	最大処方量	12 週間まで	90 日まで	4 週間まで	4 週間まで	妊娠可能な女性患者は 4 週間、その他は 12 週間まで	妊娠可能な女性患者は 4 週間、その他は 12 週間まで	妊娠可能な女性患者は 4 週間、その他は 12 週間まで

※IVR(Interactive Voice Response System)：音声自動応答システムを利用した電話による調査

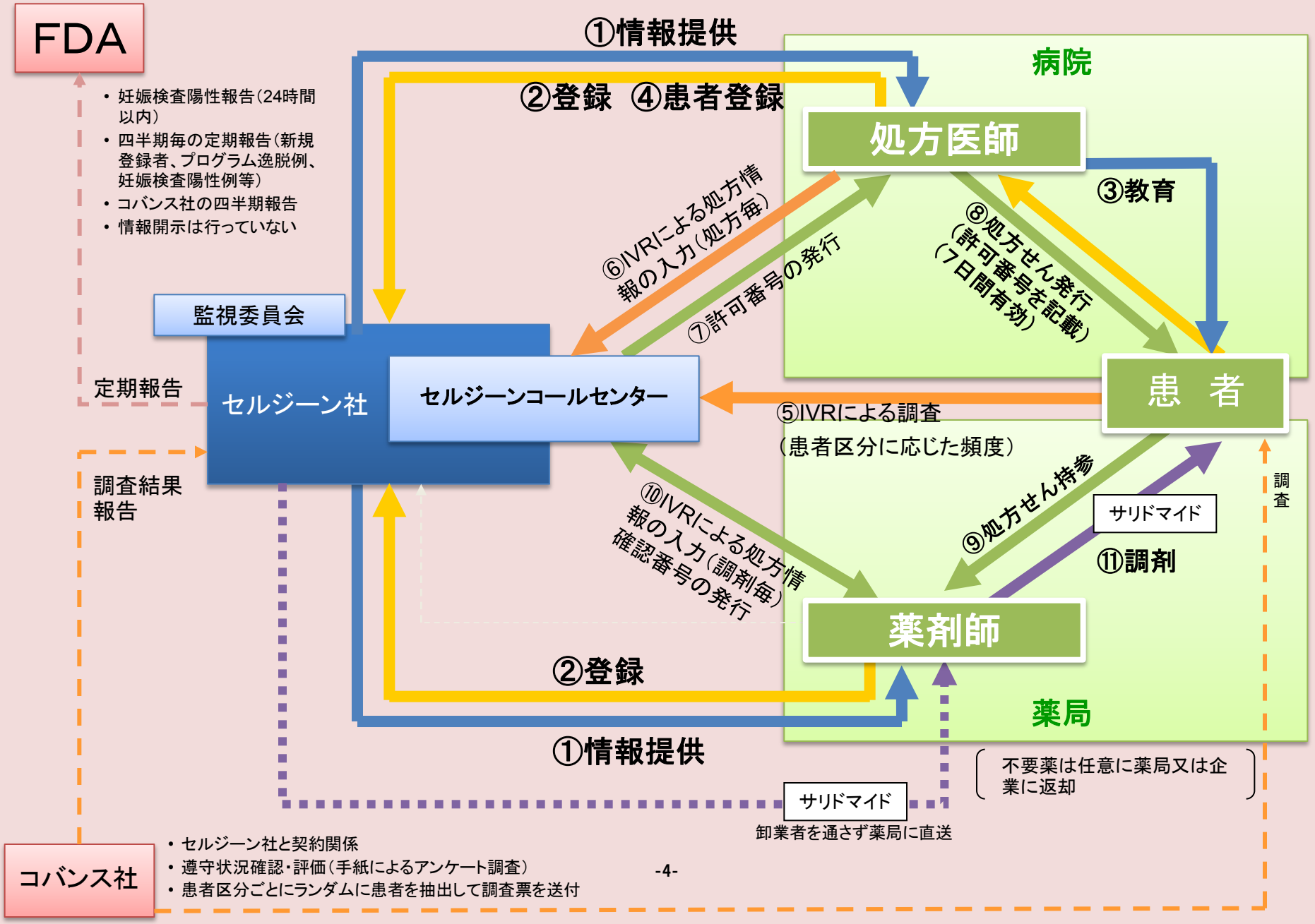
サリドマイド製剤安全管理手順（TERMS）の概要



RevMate®（レブラミド®適正管理手順）の概要



米国におけるサリドマイド安全管理システム（STEPS）の概要



EUにおけるサリドマイド及びレナリドミドの妊娠防止プログラムの実施について

１．製造販売承認時の取扱い

EUでは、サリドマイド及びレナリドミドの製造販売承認時に、欧州委員会決定（Commission Decision）という形でEU加盟国及び製造販売事業者に対してそれぞれ遵守すべき条件を課しており、これはEU加盟国及び製造販売事業者に対して法的拘束力を有している。

これを受けて各加盟国は、製品の製造販売が自国内で開始される前に、欧州委員会決定を自国で適切に実施するための方法について製造販売事業者と検討・調整を行い、両者で合意された内容に基づき妊娠防止プログラムを実施している。

欧州委員会決定に規定された内容が遵守される限りにおいては、各国の法令や医療制度等を踏まえ各国独自の方法を導入することが可能となっている。

２．各加盟国の遵守事項

欧州委員会決定で規定されている各加盟国が遵守すべきとされている事項は次のとおり。

（１）サリドマイド

① 次のことを確保するための体制について製造販売業者と合意すること。

○製造販売の開始前に、処方／調剤する予定の全ての医師／薬剤師が「医療関係者への書簡」を受け取っていること。

○処方を行う前に、処方する予定に全ての医療関係者に対して「医療関係者の教育キット」[1]（医療関係者向け冊子、患者向け冊子、患者カード[2]、製品概要、パッケージリーフレット及び表示）が提供されていること。

② 次のことを確保するための措置をとること。

○一回あたりの処方量の制限（妊娠可能女性は4週間、その他は12週間）

○処方日から7日以内に調剤

③ 製造販売事業者と妊娠防止プログラムの詳細について合意し、製造販売の開始前にそれが実施されることを確保すること。

④ 患者カードシステム（又は同等の手段）の実施について合意すること。

⑤ 製造販売事業者が自国の患者団体に教育資材の確認を依頼することを確保

---

[1] 別途、各種資材に含まれるべき情報（医師による患者説明の実施・患者向け冊子の提供・毎月の妊娠検査の実施・妊娠時の対応、妊娠可能女性患者・男性患者による避妊の実施、避妊法変更時の患者による医師への申告等）が規定されている。

[2] 適切に説明が行われたことの確認、妊娠可能性の状況、避妊実施の確認、治療開始前の妊娠検査陰性の確認、妊娠検査実施日・結果を含むとされている。

するとともに、その結果を当局に報告させ、国で最終版を確認すること。

⑥ 製造販売の開始前に、適用外使用をモニターするための方策、妊娠防止プログラムの効果／遵守状況を評価するための方策について製造販売業者と合意すること。

⑦6 ヶ月毎に妊娠防止プログラムの実施状況、使用量の推定を EMA に報告すること。

⑧ 「医療関係者への書簡」及び「医療関係者の教育キット」が所定の事項が含まれていることを確保すること。

（2）レナリドミド

上記のサリドマイドで求められている事項のうち、①③④⑥⑧が求められている（⑧については、規定されている項目に若干違いあり）。

ドイツにおける妊娠防止プログラムの概要

＊同意書にチェックリストあり。患者署名の他、医師の確認と署名あり。

セルジーン
（Celgene GmbH）

①情報提供、説明資材の提供

医療機関

②登録（T-Register）

③T-処方せんの送付

処方医師

④患者に応じた教育
（処方前に説明資料セットの交付。書面同意書＊）

⑤投与開始前及び
毎月の妊娠検査

⑥T-処方せん
の発行

疑義照会

BfArM
ドイツ連邦医薬品医療機器庁

患者

＊薬剤管理者の設置なし

＊最大処方量
妊娠可能な女性患者：4週間分
それ以外の患者：12週間分

情報公開

⑨T-処方せんの写しの送付
（四半期毎）

薬剤師

⑦T-処方せん
の確認

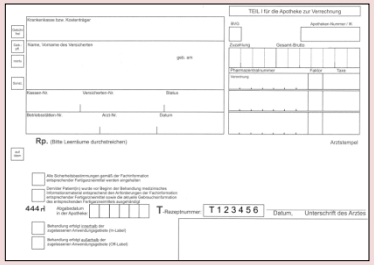
⑧薬剤交付・服薬指導

不要薬回収

薬局

定期報告（半年毎）
処方数等

EMA
欧州医薬品庁



T-処方せん

- サリドマイド及びレナリドミド専用の特別な処方せん
- T-Registerの登録を受けた医師のみに対してBfArMが送付。一枚ごとにシリアル番号 が記入され、交付時にシリアル番号と交付先医師を記録。
- ①必要な安全措置がとられていること、②患者に対して必要な情報が全て提供されていることの2点のチェック欄があり、医師が記入する。
- 2枚綴りになっており、うち1枚は薬局からBfArMに返送され、集計される。
- BfArM提出分の患者情報部分はマスキング。

T-処方せん

＊BfArM宛てに送付される写しでは、点線部分が黒塗り。

TEIL I für die Apotheke zur Verrechnung

Krankenkasse bzw. Kostenträger
健康保険又は保険会社

Gebühr frei
Geb.-pfl.
noctu
Sonst.

Name, Vorname des Versicherten
被保険者の氏名

geb. am
生年月日

Kassen-Nr. 保険番号 | Versicherten-Nr. 被保険者番号 | Status ステータス

Betriebsstätten-Nr. 事業所番号 | Arzt-Nr. 医師番号 | Datum 日付

BVG

薬局番号 Apotheken-Nummer / IK

Zuzahlung 追加支払 | Gesamt-Brutto 総額

Pharmazentralnummer 医薬品番号 | Faktor | Taxe

Verordnung 処方 | 係数 | 税

Rp. (Bitte Leerräume durchstreichen)
空欄を埋めて下さい

Arztstempel
医師の住所

aut idem

☐ Alle Sicherheitsbestimmungen gemäß der Fachinformation entsprechender Fertigarzneimittel werden eingehalten
製品の技術情報に関連するすべての安全要件が満たされている

☐ Dem/der Patient(in) wurde vor Beginn der Behandlung medizinisches Informationsmaterial entsprechend den Anforderungen der Fachinformation entsprechender Fertigarzneimittel sowie die aktuelle Gebrauchsinformation des entsprechenden Fertigarzneimittels ausgehändigt
患者は治療開始前に技術要件に従って医薬品情報及び実際の使用に必要な情報を与えられた

444H

Abgabedatum in der Apotheke: ☐☐☐☐☐☐
薬局での日付

T-処方せん番号
T-Rezeptnummer: T123456

Datum, Unterschrift des Arztes
日付 医師の署名

☐ Behandlung erfolgt innerhalb der zugelassenen Anwendungsgebiete (In-Label)

☐ Behandlung erfolgt außerhalb der zugelassenen Anwendungsgebiete (Off-Label)

イタリアにおける妊娠防止プログラムの概要

セルジーン
（Celgene Italia）

①情報提供、説明資材の提供

AIFA
イタリア医薬品庁

CIRR
処方情報登録システム

医療機関（院内処方のみ）

④患者登録

⑤処方情報
入力

処方医師

②患者に応じた教育
（処方前に説明資料セットの交付。書面同意書）

③投与開始前及び毎月の
妊娠検査（血液検査）

患者

疑義照会

＊薬剤管理者の設置なし

＊最大処方量：4週間分

薬剤師

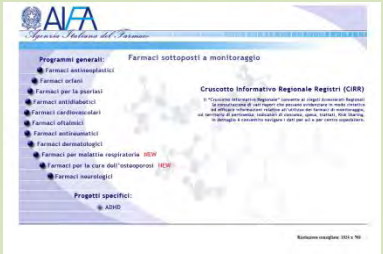
⑥薬剤交付・服薬指導

不要薬回収

定期報告（半年毎）

情報公開

EMA
欧州医薬品庁

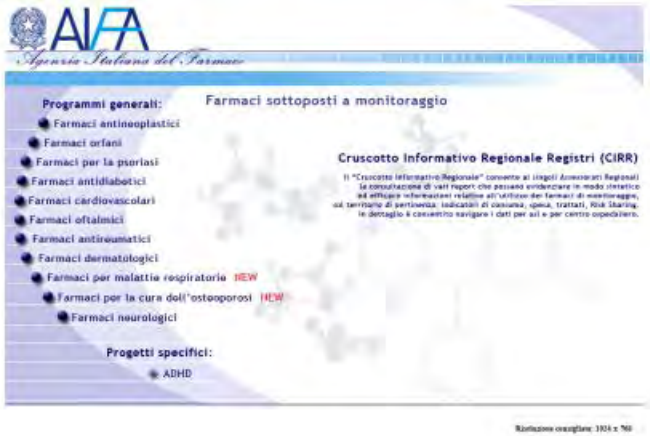


CIRR(Cruscotto Informativo Regionale Registri)処方情報登録システム

- 医薬品の処方時に、医師又は医療関係者が、患者情報や適用疾患、処方量などをインターネット経由で入力することが義務付けられている。
- サリドマイド及びレナリドミドに限らず、高価な医薬品全般が対象
- 入力項目は医薬品毎に毎なり、サリドマイド及びレナリドミドについては、妊娠防止に関するチェック事項も含まれている。処方毎に妊娠検査結果を入力する。

CIRRウェブサイト

トップ画面



処方時入力画面

MODULO DI RICHIESTA FARMACO: THALIDOMIDE

Codice identificativo Unico della Richiesta:	1260
Numero della Richiesta:	1
Centro prescrittore:	CASA DI CURA VILLALBA S.R.L. - ONCOLOGIA MEDICA -

I campi contrassegnati dall'* sono obbligatori.

dose/die raccomandata:	200mg/die per 4 settimane

一日服用量 Dose/Die richiesta: 333 mg (es 35.5 mg: usare il punto per inserire numeri decimali)

合計処方量 Dose totale richiesta*: 9324 mg (es 35.5 mg: usare il punto per inserire numeri decimali)

妊娠検査結果

Test di gravidanza*:	Sì	Se sì, esito:	Negativo	Data del test:	20 03 2009 (gg/mm/aaaa)
Test di gravidanza*:		Se sì, esito:		Data del test:	(gg/mm/aaaa)

Data richiesta farmaco*: 27 04 2009 (gg/mm/aaaa)

処方日 Data prevista per la somministrazione* : 27 04 2009 (gg/mm/aaaa)

薬局種別 Farmacia di riferimento* :
- Farmacia Ospedaliera
- Farmacia territoriale ASL di domicilio
- Altra farmacia (altra Struttura, altra ASL, ecc.)

Si ricorda che l'invio telematico delle richieste di farmaco a Farmacie diverse da quella indicata come Farmacia di riferimento del Centro prescrittore è consentito, sotto la responsabilità del Centro prescrittore, nel rispetto delle norme vigenti nazionali e regionali relativamente alle singole specialità medicinali

Procedi Cancella

患者情報入力画面

AIFA
AGENZIA ITALIANA DEL FARMACO
REGISTRO DEI FARMACI ONCOLOGICI SOTTOPOSTI A MONITORAGGIO

REGISTRAZIONE NUOVO PAZIENTE

I campi contrassegnati dall'* sono obbligatori.

Cognome*: (Inserire cognome o le prime 3 lettere)	
Nome*: (Inserire nome o le prime 3 lettere)	
Codice fiscale: (Campo obbligatorio per i farmaci: Avastin, Tarceva, Nexavar, Sutent, Sprycel, Revlimid, Revlimid 648,Atriance, Tasigna, Torisel, Vectibix, Yondelis, Thalidomide e Alimta)	

患者氏名（3文字）

Solo nel caso in cui il paziente non possieda codice fiscale inserire i dati seguenti:

Il paziente dichiara di non essere già stato sottoposto ad analogo trattamento :	Sì No
Tipo di documento di riconoscimento :	Passaporto Permesso di soggiorno Altro
Se Altro Specificare:	
Numero documento di riconoscimento:	
Nazione dell'Autorità che ha rilasciato il documento:	

In accordo alla normativa sulla privacy 196/2003, nel database globale il paziente sarà identificato dal codice che sarà assegnato automaticamente dal sistema. Nel database ad uso locale il paziente potrà essere identificato da cognome, nome o iniziali

Data di nascita*:	(gg/mm/aaaa)
Sesso:*	M F
Luogo di nascita* (Comune)	☐ Estero
Regione (compilata automaticamente):	
Numero Cartella Clinica:	
ASL di residenza del Paziente*:	
ASL di domicilio diversa da quella di residenza*:	Sì No

生年月日

性別

出生地

居住地の保健所

居住地以外の保健所

Registrazione- Thalidomide Celgene 1/2

※これらは入力画面の一部であり、この他にも、催奇形性リスクや献血の禁止等に関する説明の有無の入力画面等がある。

ANNEX

CONDITIONS OR RESTRICTION WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

The Member States must ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

1. The Member States shall agree the details of a controlled distribution system with the MAH according to national regulations and healthcare systems and must implement such programme nationally to ensure that:
    - Prior to launch, all doctors and pharmacists who intend to prescribe or dispense Thalidomide Celgene receive a Dear Healthcare Professional letter as described below.
    - Prior to prescribing all healthcare professionals who intend to prescribe (and in agreement with the National Competent Authority, dispense) Thalidomide Celgene are provided with an Educational Healthcare Professional's Kit containing the following:
        - Healthcare professional booklet
        - Patient booklets
        - Patient cards
        - Summary of Product Characteristics, Package Leaflet and Labelling

2. The Member States shall put into place measures to ensure that:
    - The maximum treatment duration for one prescription shall be
        - 4 weeks for women with childbearing potential
        - 12 weeks for men and women without childbearing potential
    - Prescriptions can only be dispensed within 7 days of the date of the prescription

3. The Member States shall ensure that the MAH implements a pregnancy prevention programme (PPP) within their territory. Details of how the PPP will be implemented should be agreed with the Marketing Authorisation Holder and put in place prior to the marketing of the product.

4. The Member States should agree the local implementation of the patient card system

5. The Member States should ensure that the MAH provides the educational materials to the national patients' organisations for review or if such an organisation does not exist or can not be involved, to a relevant patients group. Patients involved should be preferably naïve to the history of thalidomide. Results of the user testing will have to be provided to the national competent authority and final materials validated at a national level.

6. The Member State should agree with the Marketing Authorisation Holder prior to the launch of the product:
    - The most appropriate strategies to monitor the off label use within national territory
    - The collection of detailed data with at least patient demographics and indication in order to monitor closely the off-label use within national territory
    - The set-up of national measures to assess the effectiveness of and compliance with the PPP.

7. The Member States shall report to the EMEA the following information at 6 monthly intervals following the Commission Decision:
    - The status of implementation of the PPP within their MS
    - Estimates of usage in their MS

8. The Member States shall ensure that the following key elements are included in the appropriate material:

Dear Healthcare Professional letter

The Dear Healthcare Professional letter will consist of two parts:

- Core text as agreed by the CHMP
- National specific requirements agreed with the National Competent Authority regarding:
    - Distribution of the product
    - procedures to ensure that all appropriate measures have been performed prior to thalidomide being dispensed

Educational healthcare professional's kit

The Educational healthcare professional's kit shall contain the following elements:

- Healthcare professional booklet
    - History of thalidomide, background on Thalidomide Celgene and its licensed indication
    - Posology
    - Maximum duration of prescription
        - 4 weeks for women with childbearing potential
        - 12 weeks for men and women without childbearing potential
    - Teratogenicity and the need to avoid foetal exposure
    - Obligations of healthcare professionals who intend to prescribe or dispense Thalidomide Celgene including
        - The need to provide comprehensive advice and counselling to patients
        - That patients should be capable of complying with the requirements for the safe use of thalidomide
        - Need to provide patients with the appropriate patient educational material
        - Report any pregnancy, neuropathy or other adverse events to Celgene and the local health authority using the forms provided in the "Educational Healthcare Professional's Kit" (if applicable to a Member State)

    - Safety Advice relevant to all patients
        - Description and management of thromboembolic and cardiovascular events, and peripheral neuropathy
        - Disposal of unwanted medicine
        - Not to donate blood during treatment and for one week after treatment ends

    - Algorithm for Pregnancy Prevention Plan implementation
        - This shall assist with patient categorisation, and determination of required pregnancy prevention and testing measures.

    - Pregnancy Prevention Programme information
        - Definition of women with childbearing potential (WCBP) and actions the prescriber should take if childbearing status is unclear
        - Information on what is effective contraception
        - Safety advice for WCBP
            - Need to avoid foetal exposure
            - Pregnancy prevention requirement, definition and need for adequate contraceptive methods
            - That if she needs to change or stop using her method of contraception she should inform:
              - the physician prescribing her contraception that she is on thalidomide
              - the physician prescribing thalidomide that she has stopped or changed her method of contraception
            - Pregnancy testing requirements
                - Advice on suitable tests

        - Frequency (before commencing, monthly during treatment and after finishing treatment)
    - Need to stop Thalidomide Celgene immediately upon suspicion of pregnancy
    - Need to tell treating doctor immediately upon suspicion of pregnancy
- <u>Safety advice for men</u>
    - The need to avoid foetal exposure
    - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not using effective contraception
    - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom during intercourse
    - That he should not donate semen during therapy and for one week following discontinuation of thalidomide

- Pregnancy reporting requirements
    - Stop Thalidomide Celgene immediately upon suspicion of pregnancy
    - Refer patient to physician specialised or experienced in dealing with teratology for advice and evaluation
    - Complete pregnancy reporting form as provided in the "Educational Healthcare Professional's Kit"
    - Local contact details for reporting of any suspected pregnancy

- Pregnancy initial and outcome reporting forms
- Post-marketing and compliance assessment (as applicable to a Member State)
- Neuropathy and adverse reaction reporting forms

- Treatment initiation forms
    - There should be 3 types of treatment initiation forms:
        - Female patient of childbearing potential
        - Female patient of non-childbearing potential
        - Male patient

    - All treatment initiation forms should contain the following elements:
        - Teratogenicity warning
        - Date of counselling
        - Affirmation of patient understanding regarding the risk of thalidomide and the PPP measures.
        - Patient details, signature and date
        - Prescriber name, signature and date
        - Aim of this document i.e. as stated in the PPP: "The aim of the treatment initiation form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of thalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

    - Treatment initiation forms for female patients with childbearing potential should also include:
        - Confirmation that the physician has discussed the following:
            - The need to avoid foetal exposure
            - That if she is pregnant or plans to be, she must not take Thalidomide Celgene
            - The need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment

- That if she needs to change or stop using her method of contraception she should inform:
  - the physician prescribing her contraception that she is on thalidomide
  - the physician prescribing thalidomide that she has stopped or changed her method of contraception
- The need for pregnancy tests i.e. before treatment, every 4 weeks during treatment and after treatment
- The need to stop Thalidomide Celgene immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy
- That she should not share the treatment with any other person
- That she should not donate blood during therapy and for one week following discontinuation of thalidomide
- That she should return the capsules to the pharmacist at the end of treatment

- Treatment initiation forms for female patients with no childbearing potential should also include:
  - Confirmation that the physician has discussed the following:
    - That she should not share the treatment with any other person
    - That she should not donate blood during therapy and for one week following discontinuation of thalidomide
    - That she should return the capsules to the pharmacist at the end of treatment

- Treatment initiation forms for male patients should also include:
  - Confirmation that the physician has discussed the following:
    - The need to avoid foetal exposure
    - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not on effective contraception
    - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
    - That he should not donate blood or semen during therapy and for one week following discontinuation of thalidomide
    - That he should not share the treatment with any other person
    - That he should return the capsules to the pharmacist at the end of treatment

- Patient cards and/or equivalent tools:
  - verification that appropriate counselling has taken place
  - documentation of childbearing status potential
  - check box (or similar) which physician ticks to confirm that patient is using effective contraception (if female with childbearing potential)
  - verification of initial negative pregnancy test prior to start of treatment (if female with childbearing potential)
  - pregnancy test dates and results

- Education booklets for patients:
  - The booklets can be of 3 types or a single patient booklet that combines the information for each patient category:
    - Booklet for women of childbearing potential and their partners
    - Booklet for women patients who are not of childbearing potential

- Booklet for male patients

- All booklets should contain the following information
  - That Thalidomide Celgene is teratogenic
  - That Thalidomide Celgene may cause thromboembolism, cardiovascular events and neuropathy
  - Description of the patient card and its use in the individual Member State
  - National or other applicable specific arrangements for a prescription for thalidomide to be dispensed
  - That Thalidomide Celgene must not be given to any other person
  - That the patient should not donate blood during therapy and for one week following discontinuation of thalidomide
  - That the patient should tell their doctor about any adverse events
  - That any unused capsules should be returned to the pharmacist at the end of the treatment

- The following information should also be provided in the appropriate booklet
  - Female patient of childbearing potential
    - The need to avoid foetal exposure
    - The need for effective contraception
    - That if she needs to change or stop using her method of contraception she should inform:
      - the physician prescribing her contraception that she is on thalidomide
      - the physician prescribing thalidomide that she has stopped or changed her method of contraception
    - The need for pregnancy tests i.e. before treatment, every 4 weeks during treatment and after treatment
    - The need to stop Thalidomide Celgene immediately upon suspicion of pregnancy
    - The need to contact their doctor immediately upon suspicion of pregnancy
  - Male patients
    - The need to avoid foetal exposure
    - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not on effective contraception
    - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
    - That he should not donate semen during therapy and for one week following discontinuation of thalidomide.

ANNEX

1

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES**

The Member States must ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

1. The Member States shall agree the details of a controlled distribution system with the MAH according to national regulations and healthcare system and must implement such programme nationally to ensure that:
   - Prior to launch, all doctors who intend to prescribe Revlimid and all pharmacists who may dispense Revlimid receive a Direct Healthcare Professional Communication as described below.
   - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Revlimid are provided with a physician information pack containing the following:
     - Educational Health Care Professional's kit
     - Educational brochures for Patients
     - Patient cards
     - Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.

2. The Member States shall ensure that the MAH implements a pregnancy prevention programme (PPP) within their territory. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.

3. The Member States should agree the final text of the Direct Healthcare Professional Communication and the physician information pack contents with the MAH and ensure that the materials contain the key elements as described below.

4. The Member States should agree the local implementation of the patient card system.

5. The Member States should also agree with the MAH prior to the launch of the product:
   - The feasibility of collecting detailed data relating to the indication in order to monitor closely the off-label use within the national territory.
   - The set-up of national measures to assess the effectiveness of and compliance with the PPP

Key elements to be included

Direct Healthcare Professional Communication

The Direct Healthcare Professional Communication shall consist of two parts:
- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:
  - Distribution of the product
  - To ensure that all appropriate measures have been performed prior to Revlimid being dispensed

The Educational Healthcare Professional's Kit

The Educational Health Care Professional's Kit shall contain the following elements:
- Brief background on lenalidomide and its licensed indication
- Posology
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans including a summary of the results of study CC-5013-TOX-004

- Obligations of the health care professional in relation to the prescribing of Revlimid
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of Revlimid
    - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
    - Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
    - Description and management of thromboembolic risk including incidence rates from clinical trials and post-marketing experience
    - Use in patients with hepatic and/or renal impairment
    - Disposal of unwanted medicine
    - Local country specific arrangements for a prescription for Revlimid to be dispensed
    - Description of risk of hypothyroidism
    - Explanation of unknown risk of neuropathy with long term use
- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of PPP
    - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
    - The need to avoid foetal exposure
    - Description of the PPP
    - Need for adequate contraception (even if woman has amenorrhoea) and definition of adequate contraception
    - Pregnancy test regime
        - Advice on suitable tests
        - Before commencing treatment
        - During treatment based on method of contraception
        - After finishing treatment
    - Need to stop Revlimid immediately upon suspicion of pregnancy
    - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
    - The need to avoid foetal exposure
    - The need to use condoms if sexual partner is pregnant or a WCBP (even if man has had a vasectomy)
        - During Revlimid treatment
        - For one week following final dose.
    - That if his partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop Revlimid immediately upon suspicion of pregnancy
    - Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy
    - Pregnancy reporting form
- Check list for physicians ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status
- Adverse event reporting forms

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential and their partners
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:

- That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans.
- That Revlimid may cause neutropenia and thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- National or other applicable specific arrangements for a prescription for Revlimid to be dispensed
- That the patient should not give Revlimid to any other person
- That the patient should not donate blood
- That the patient should tell their doctor about any adverse events

The following information should also be provided in the appropriate brochure:

<u>Brochure for women patients with childbearing potential</u>

- The need to avoid foetal exposure
- Description of the PPP
- Need for adequate contraception and definition of adequate contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Revlimid immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

<u>Brochure for male patients</u>

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP (even if man has had vasectomy)
    - During Revlimid treatment
    - For one week following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately

<u>Patient Card</u>

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing status potential
- Pregnancy test dates and results