EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Risk Management

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Topics

Some Pharmacovigilance concepts

Why don’t we know all the side effects of a medicine?

What are the new requirements for risk management plans

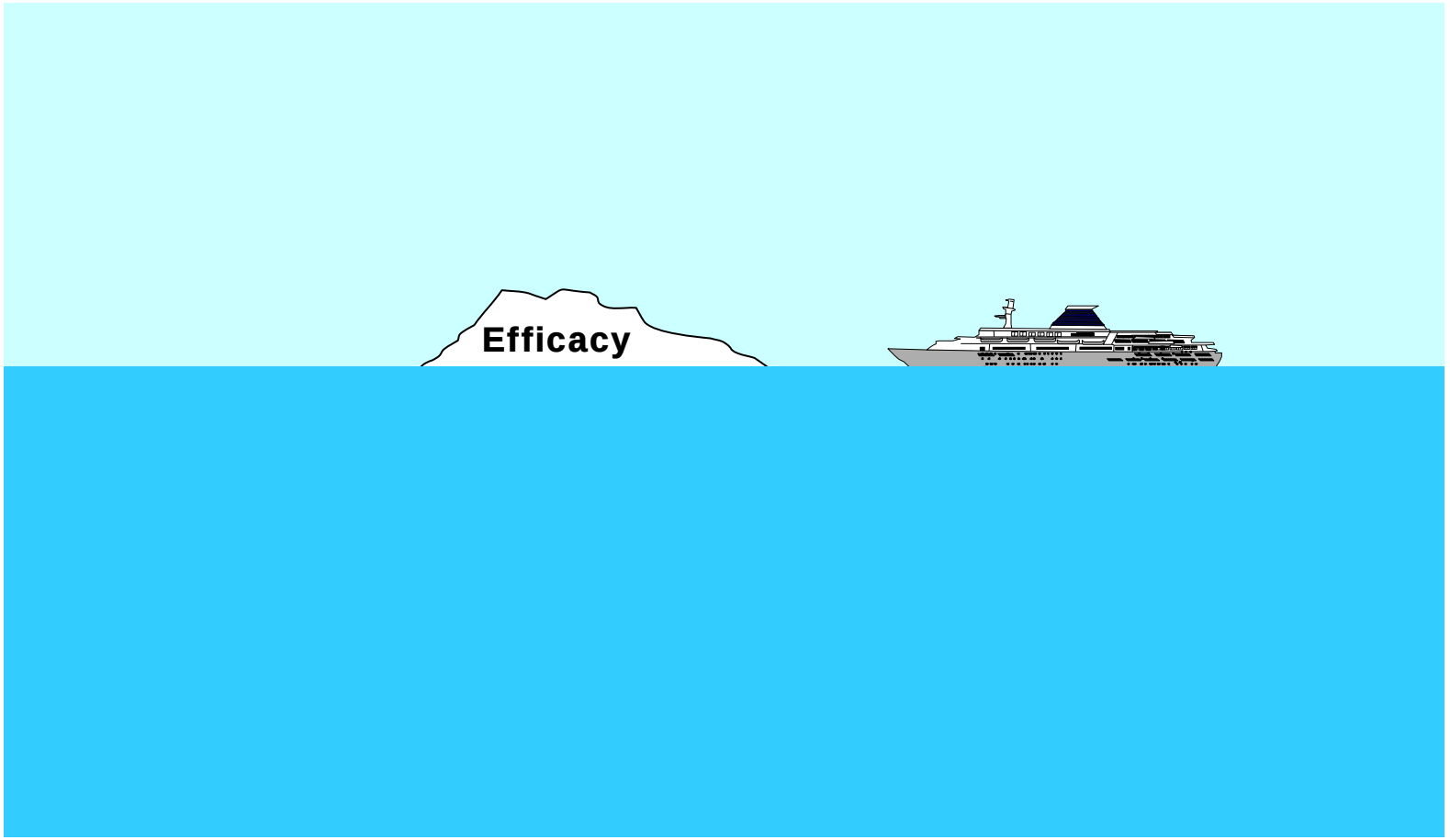
What does a risk management plan look like

How does it affect patients?

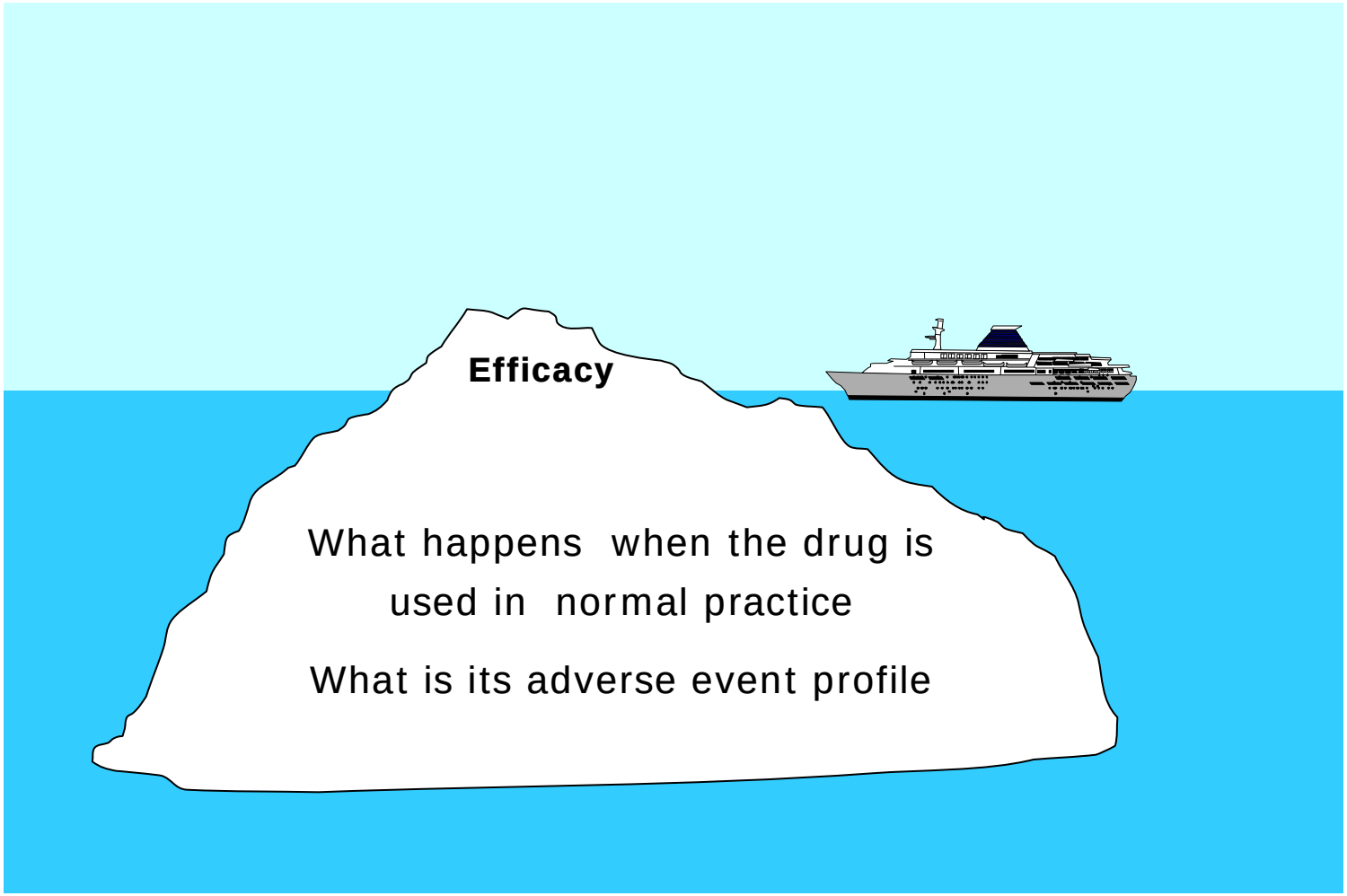
The Drug Development Programme

- Cost of $1.3 - $11 billion
- Median time 11 years
  (range 3 - > 25 years)
- Median 1480 patients exposed
  (range 129 - 9,400)

What we know at the end of the clinical trial programme



What we don't know



People often excluded from clinical trials

- Young
- Elderly
- Women of childbearing age
- Pregnant women
- Certain ethnic groups

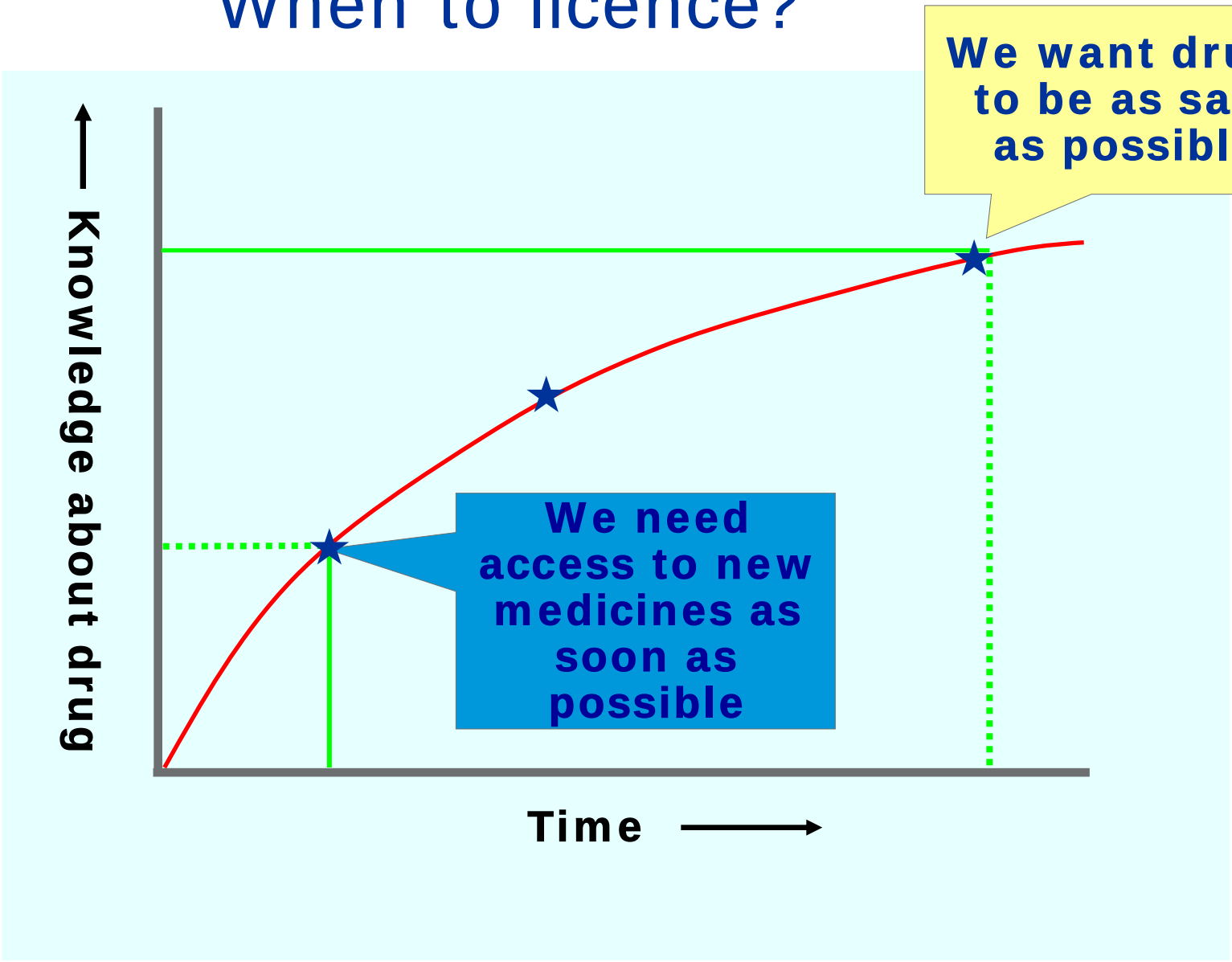
People often excluded from clinical trials

- people with concomitant disease
  - cardiac disease
  - renal disease
  - hepatic disease
  - multiple impairments
- people on concomitant medication

Other ADRs which are unlikely to be identified in clinical trials

- adrs which have a long latency
- adrs which need prolonged exposure
- adrs due to cumulative effects
- adrs which are rare
- adrs which mimic common diseases

When to licence?



The Positive Benefit Risk Balance

What we actually mean

At the time the medicine is authorised, the benefits outweigh the risks for the average patient in the approved indication

The Risk management System

Definition:

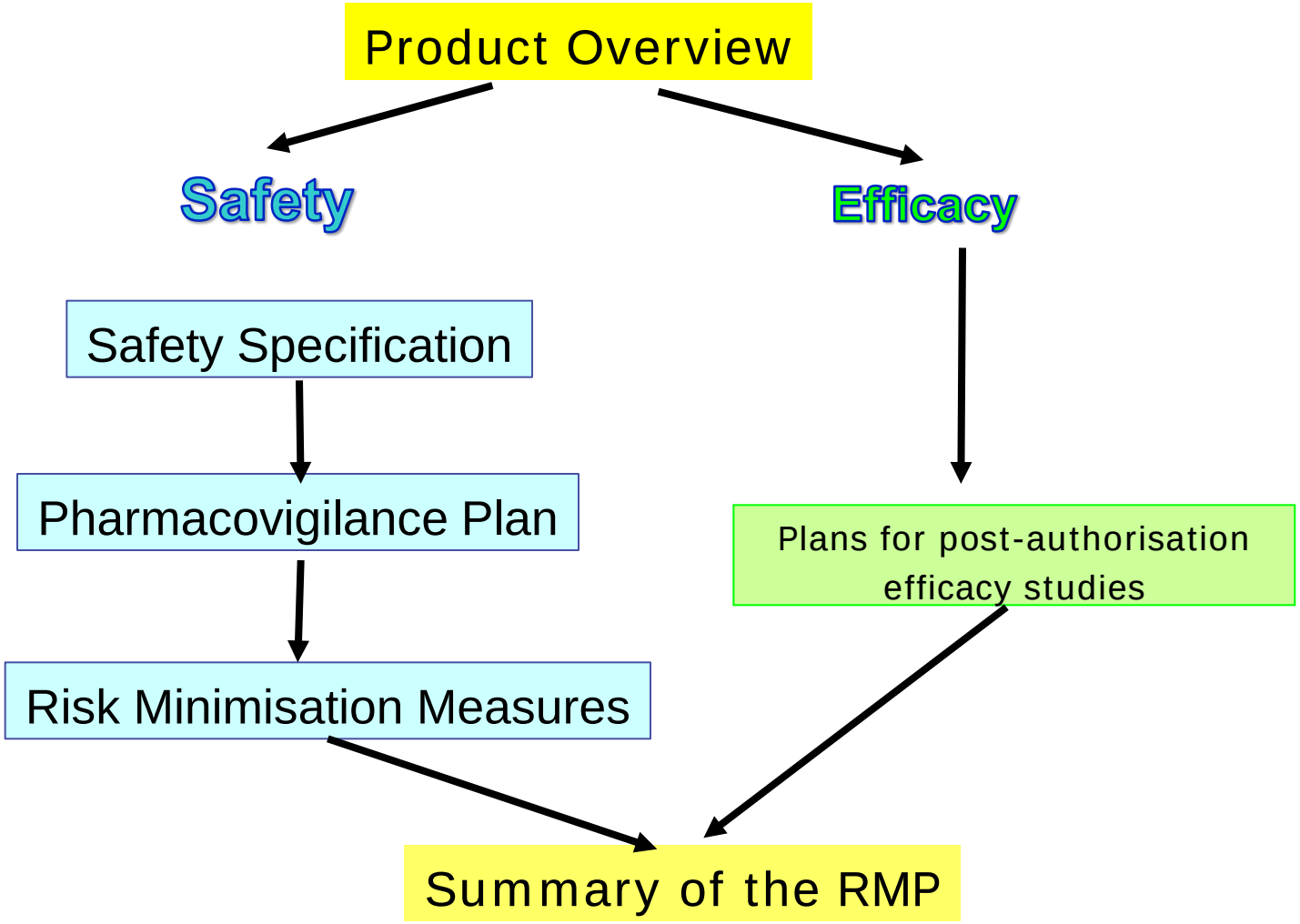
a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions

New RMP structure

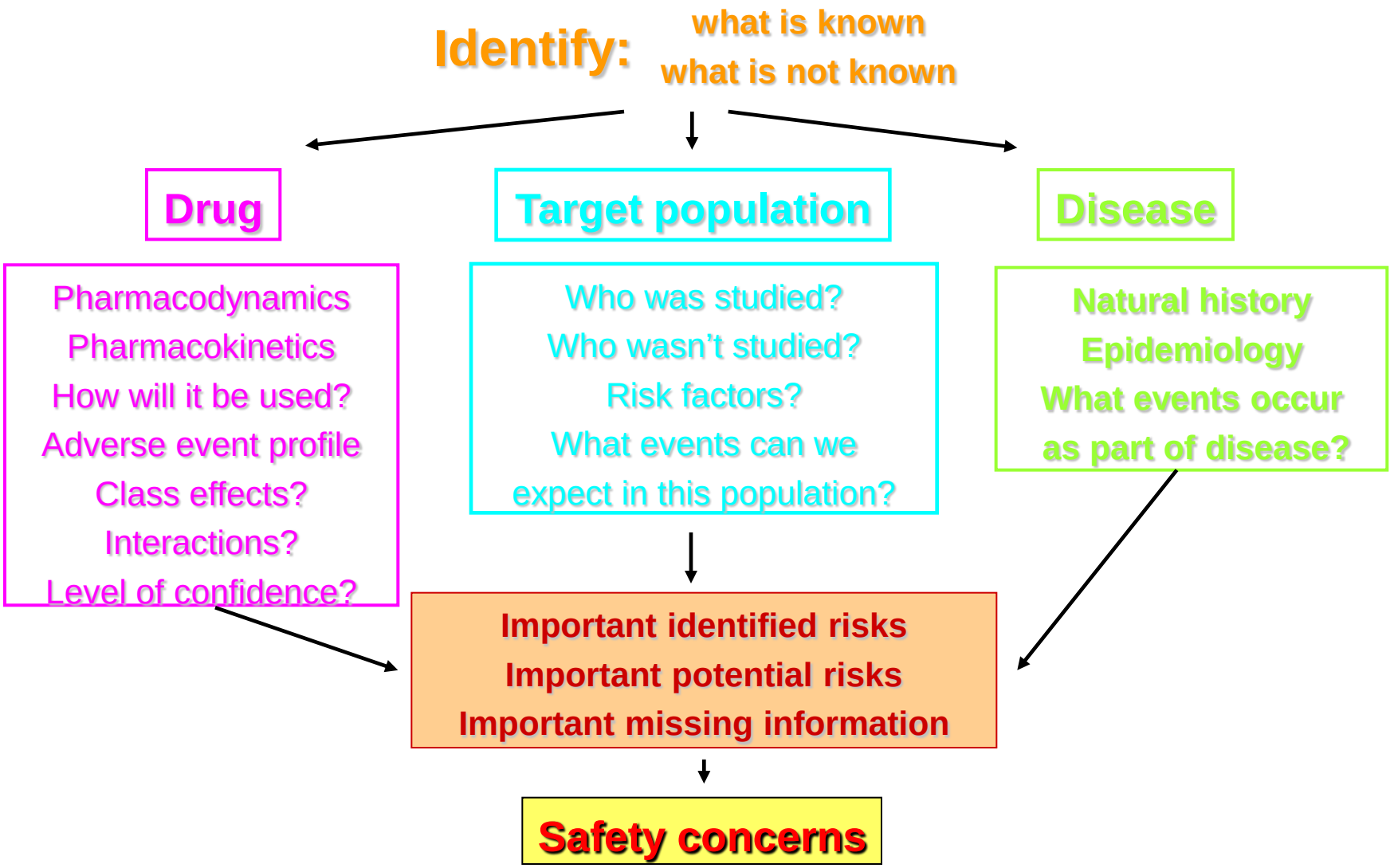
Part I	Product(s) Overview
Part II	Safety Specification
Part III	Pharmacovigilance Plan
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk Minimisation Measures
Part VI	Summary of the RMP
Part VII	Annexes

RMP is substance based

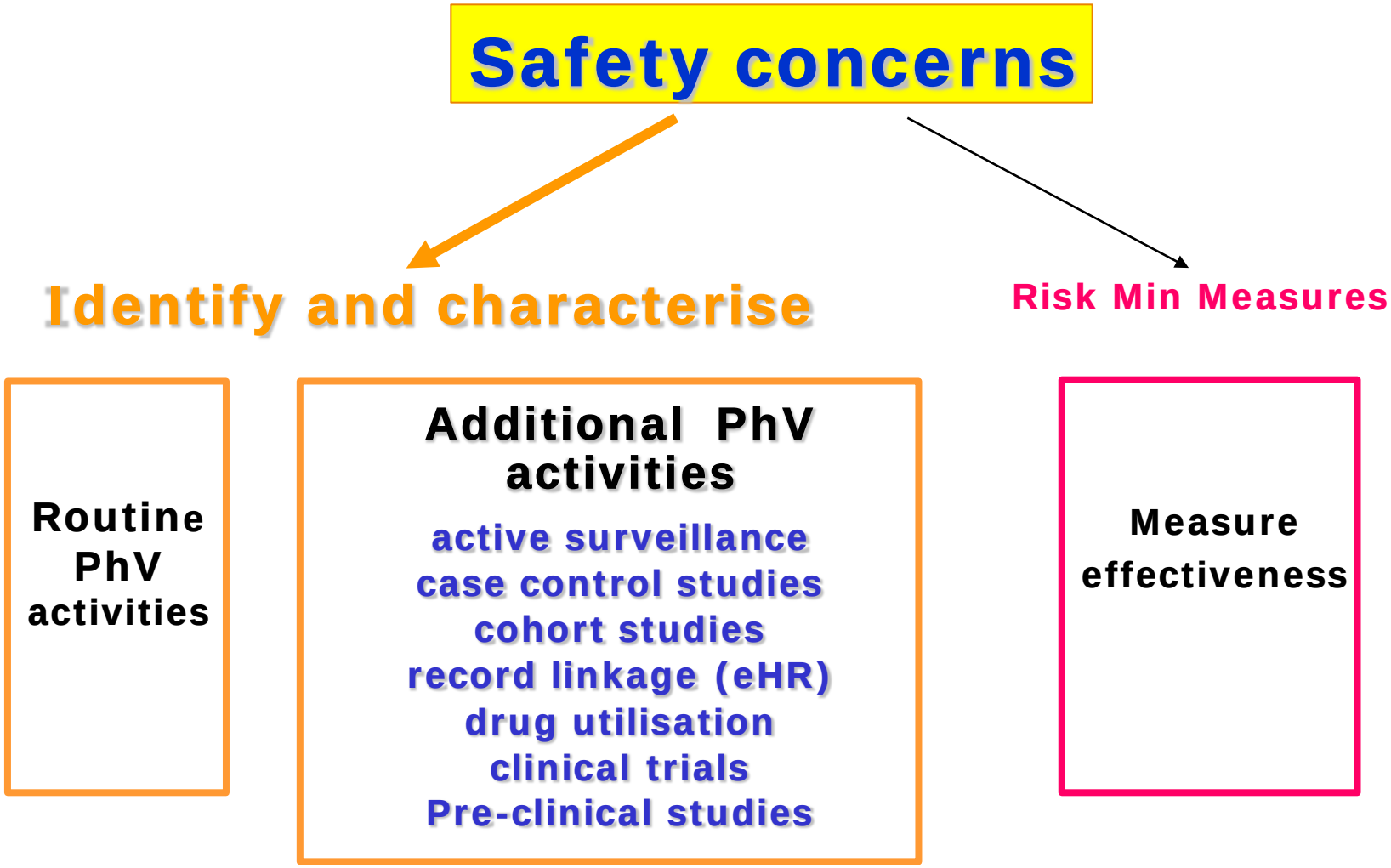
Information Flow in the RMP



Safety specification



Part III: Pharmacovigilance Plan



Part IV: Plans for post-authorisation efficacy studies

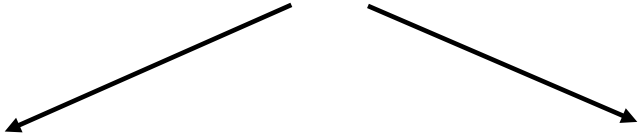
Applicability of efficacy to all patients in the target population

List of post-authorisation efficacy studies

Part V: Risk Minimisation Measures

Safety concerns

Prevent or minimise



Routine risk minimisation

- Legal status
- Pack size
- SPC
- Package leaflet
- Labelling

Additional Risk Minimisation

Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Fareston 60 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 mg toremifene (as citrate).

Excipients: 30 mg lactose per tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, round, flat, bevelled edge tablet with TO 60 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

First line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients.
Fareston is not recommended for patients with estrogen receptor negative tumours.

4.2 Posology and method of administration

Posology

The recommended dose is 60 mg daily.

Renal impairment
No dose adjustment is needed in patients with renal insufficiency.

Hepatic impairment
Toremifene should be used cautiously in patients with liver impairment (see section 5.2).

Pediatric use
There is no relevant indication for use of Fareston in children.

Method of administration

Toremifene is administered orally. Toremifene can be taken with or without food.

4.3 Contraindications

- Pre-existing endometrial hyperplasia and severe hepatic failure are contra-indications in long-term use of toremifene.
- Hypersensitivity to toremifene or to any of the excipients.
- Both in preclinical investigations and in humans, changes in cardiac electrophysiology have been observed following exposure to toremifene, in the form of QT prolongation. For reasons of drug safety, toremifene is therefore contraindicated in patients with:
  - Congenital or documented acquired QT prolongation
  - Electrolyte disturbances, particularly in uncorrected hypokalaemia
  - Clinically relevant bradycardia
  - Clinically relevant heart failure with reduced left-ventricular ejection fraction

- Previous history of symptomatic arrhythmias.

Toremifene should not be used concurrently with other drugs that prolong the QT interval (see also section 4.5).

4.4 Special warnings and precautions for use

Gynaecological examination should be performed before treatment administration, closely looking at pre-existing endometrial abnormality. Afterwards gynaecological examination should be repeated at least once a year. Patients with additional risk of endometrial cancer, e.g. patients suffering from hypertension or diabetes, having high BMI (>30) or history of hormone replacement therapy should be closely monitored (see also section 4.8).

Patients with a history of severe thromboembolic disease should generally not be treated with toremifene (see also section 4.8).

Fareston has been shown to prolong the QTc interval on the electrocardiogram in some patients in a dose-related manner. The following information regarding QT-prolongation is of special importance (for contraindications see section 4.3).

A QT clinical study with a 5-arm parallel design (placebo, moxifloxacin 400 mg, toremifene 20 mg, 80 mg, and 300 mg) has been performed in 250 male patients to characterize the effects of toremifene on the QTc interval duration. The results of this study show a clear positive effect of toremifene in the 80 mg group with mean prolongations of 21 - 26 ms. Regarding the 20 mg group, this effect is significant as well, according to ICH guidelines, with upper confidence interval of 10 - 12 ms. These results strongly suggest an important dose-dependent effect. As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Fareston should be used with caution in patients with ongoing proarrhythmic conditions (especially elderly patients) such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular arrhythmias (incl. Torsade de pointes) and cardiac arrest (see also section 4.3).
If signs or symptoms that may be associated with cardiac arrhythmia occur during treatment with Fareston, treatment should be stopped and an ECG should be performed.

If the QTc interval is > 500 ms, Fareston should not be used.

Patients with non-compensated cardiac insufficiency or severe angina pectoris should be closely monitored.

Hypercalcemia may occur at the beginning of toremifene treatment in patients with bone metastasis and thus these patients should be closely monitored.

There are no systematic data available from patients with labile diabetes, from patients with severely altered performance status or from patients with cardiac failure.

Fareston tablets contain lactose (30 mg/tablet). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

An additive effect on QT interval prolongation between Fareston and the following drugs and other medicinal products that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including Torsade de pointes. Therefore co-administration of Fareston with any of the following medicinal products is contraindicated (see also section 4.3):
- antiarrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide) or
- antiarrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide),
- neuroleptics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride),

Package leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Victoza 6 mg/ml solution for injection in pre-filled pen
Liraglutide

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. WHAT VICTOZA IS AND WHAT IT IS USED FOR

Victoza contains the active substance liraglutide. It helps your body reduce your blood sugar level only when blood sugar is too high. It also slows food passage through your stomach.

Victoza is used to treat type 2 diabetes mellitus when:
- metformin or a sulphonylurea alone (such as glimepiride or glibenclamide) despite the maximal tolerated dose are not enough to control your blood sugar levels.
- metformin in combination with a sulphonylurea (such as glimepiride or glibenclamide) or metformin in combination with a glitazone (such as rosiglitazone or pioglitazone) are not enough to control your blood sugar levels.

2. BEFORE YOU USE VICTOZA

Do not use Victoza
- if you are allergic (hypersensitive) to liraglutide or any of the other ingredients of Victoza (listed in section 6, 'What Victoza contains').

Take special care with Victoza
- if you are also taking a sulphonylurea (such as glimepiride or glibenclamide), your doctor may tell you to test your blood sugar levels. This will help your doctor to decide if the dose of the sulphonylurea needs to be changed.

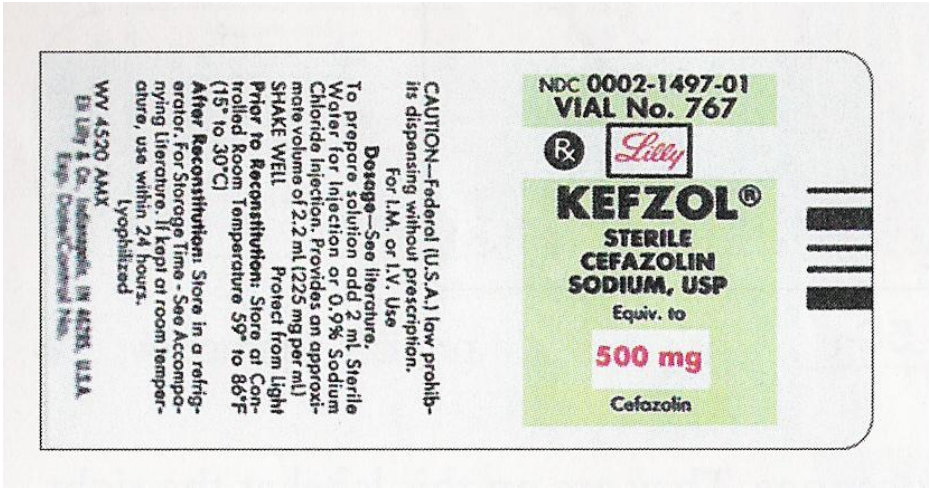
Victoza should not be used if you have type 1 diabetes or diabetic ketoacidosis. Victoza should not be used in children and adolescents under 18 years.

The use of Victoza is not recommended in patients with inflammatory bowel disease and/or diabetic gastroparesis.

If you have symptoms of acute pancreatitis, like persistent, severe abdominal pain, you should consult your doctor.

Using other medicines
Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other

Product Labelling



Part V: Risk Minimisation Measures

Safety concerns

Prevent or minimise

Routine risk

Package leaflet
Labelling

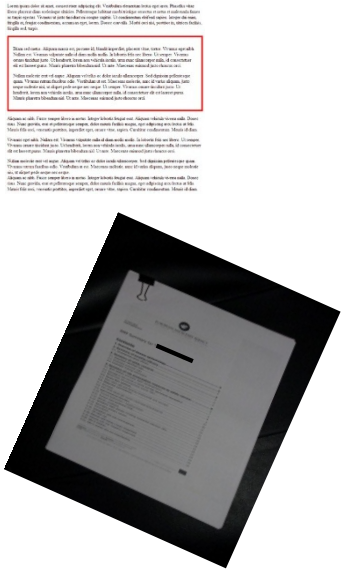
Additional Risk Minimisation measures

Controlled distribution
Educational material
Patient alert card
Patient monitoring card
Training programmes

Summary of the RMP

Possible options/tools to communicate information on the RMP

1. Updated EPAR summary template
   - Incorporate key information on the main safety concerns and measures taken to mitigate the risk



2. Produce a stand-alone RMP summary in lay language

3. Tabulated information in the assessment report

How does the RMP affect patients?

As a patient

Routine risk minimisation

Additional risk minimisation

Providing input into the RMP

Is the risk too great or should patients have the choice?

Balancing needs for access with needs to minimise risk

Is the educational material understandable?