Life-cycle approach to error prevention – an overview

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Outline of session

- Identifying the risk of medication error:
  - pre-licensing
  - changes to marketing authorisations
  - post-marketing
- approaches to risk minimisation
  - content and presentation of materials
  - how to reach the audience

Identifying risk of medication error pre-licensing

- During clinical development, consider:
  - Product design (formulation, administered via device, ease of use)
  - Context of already-available products (potential for mix-ups, familiarity of use)
  - Reports of medication errors in clinical trials (use-related AEs, difficulties using drug-device combination products)
- **Capture in risk management plan** and describe what was reported in clinical development, and how this was addressed through changes in product design, labelling, packaging etc
- Consider/propose risk minimisation measures as appropriate – is describing in product information enough?

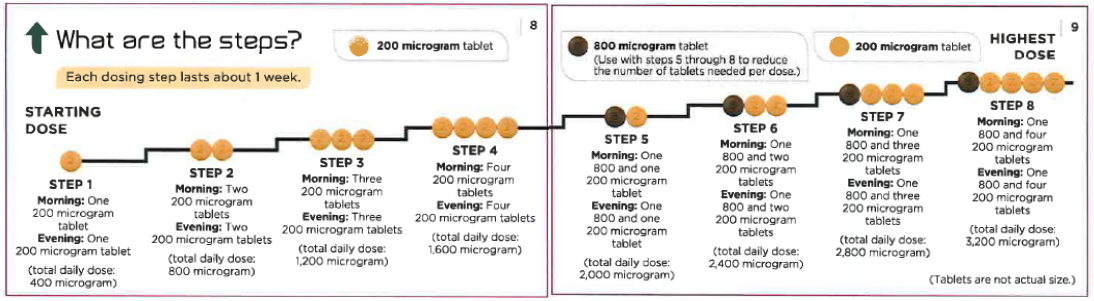
Different approaches to risk minimisation

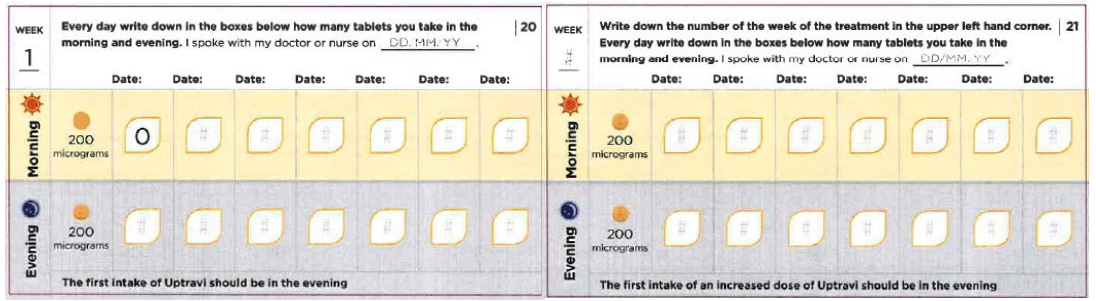
- Routine risk minimisation measures:
  - Product information (SmPC, product labelling and PIL/TIL)
  - Pack size (limited # doses: patients must regularly consult HCP)
  - Legal status:
    - prescription status;
    - restricted [hospital-only or specialist use only]
    - special [narcotics/may be abused]

- Additional measures:
  - Pregnancy prevention plans
  - Controlled/restricted access programs
  - Educational measures (e.g. patient cards, posters, pamphlets, videos)
  - Effective and transparent communications

Case studies of risk of medication errors identified at time of licensing – Uptravi (selexipag)

- Uptravi indicated in pulmonary arterial hypertension, each patient up-titrated to the highest individually tolerated dose (200µg - 1600µg twice daily)
- Potential risk of medication error: availability of 8 different dosage strengths (200µg, 400µg, 600µg, 800, µg, 1000 µg, 1200 µg, 1400 µg, 1600 µg)
- Risk minimisation measures:
  - **Routine**: titration packs include only 200µg and 800µg tablet strengths; each tablet strength is a different colour, presented in appropriately-coloured packaging
  - **Additional**: Prescriber kit for HCPs (including titration guide for HCPs, titration guide for patients which includes patient diary)





  - **Additional**: Controlled access system: aids distribution of prescriber kits to prescribers

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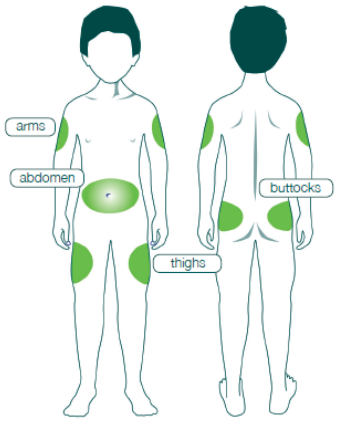
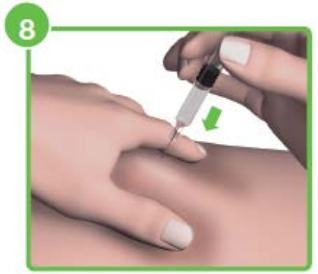
Case studies of risk of medication errors identified at time of licensing – Strensiq (asfotase alfa)

- Strensiq indicated in long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease
- used in growing children, dose adjusted frequently according to bodyweight, available in 2 strengths and 5 volumes: increased risk of medication errors
- Risk minimisation measures:
  - **Routine**: colour-coded carton/vial labels 12mg/0.3ml 18mg/0.45ml 28mg/0.7ml 40mg/1ml 80mg/0.8ml
  - **Routine**: SmPC/PIL contain dosing chart for use in dose conversion
  - **Additional**: Self-injection guide for patients, Injection guide for parents or caregivers with infant patients



Always use a new vial and carefully examine the liquid to make sure it is clear and contains no particles.

Remove the protective cap (shown as red on the image) from the vial to reveal the sterile rubber seal.



Holding the syringe like a pencil or a dart, insert the needle into the raised skin so it is at an angle of between 45º and 90º to the skin surface. For patients who have little subcutaneous fat or thin skin, a 45º angle may be preferable.

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Case studies of risk of medication errors identified at time of licensing – Ionsys (fentanyl)

- Ionsys used to control moderate to severe pain after an operation in adults in hospital
- dosing button could be pushed by someone who is not the patient (overdose, accidental exposure) and risk of accidental exposure to fentanyl in system by HCPs and patients
- Risk minimisation measures:

- **Routine**: Medicinal product subject to special and restricted medical prescription
- **Routine**: SmPC/PIL includes info on assembly, application site preparation, application, patient instruction, removal and disposal (PIL includes instruction sheet for HCPs)
- **Additional**: HCP educational programme, including:
  - importance of HCP ensuring patient knows how to use system, and that only he/she can press the dosing button;
  - checklist for monitoring inadequate product disposal to minimise risk of accidental exposure

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Identifying risk of medication error with changes to MA

- May be identified in relation to changes to/introduction of new:
  - product name
  - concentration or strength
  - pharmaceutical form
  - composition
  - method of preparing for administration
  - route of administration
  - administration device (or method of supply of administration device)
  - patient population or indication
  - inbuilt distinguishing features in terms of appearance (e.g. appearance of insulin pen device).
- **Capture in risk management plan** and describe what errors may be introduced through change to MA, and how this will be addressed through changes in product design, labelling, packaging etc
- Consider/propose risk minimisation measures as appropriate – is describing in product information enough? How to communicate to HCPs/patients?

Case studies of risk of medication errors identified in change to MA – Flolan (epoprostenol)

- Flolan is indicated in pulmonary arterial hypertension and in haemodialysis in emergency situations when heparin cannot be used
- new formulation (with solvent pH 12) has differences in storage and administration from the existing formulation (with solvent pH 10.5) - overlap in availability of new formulation
- Risk minimisation measures:
  - Routine: warning on external carton; different coloured cartons/vial caps for existing and new presentation

  - Additional: Direct Healthcare Professional Communication, advising HCP to use cold packs with Solvent pH 10.5, be clear about which formulation is prescribed/dispensed, ensure patients receive advice
  - Additional: educational materials for HCPs (checklist) and patients

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Case studies of risk of medication errors identified in change to MA – Humalog (insulin lispro)

- Humalog is indicated in treatment of adults with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis
- availability of new strength of 200 units/ml, potential for medication error due to manual transfer of insulin to a different delivery system, unnecessary dose conversion when changing from 100 units/mL to 200 units/mL or vice versa

- Risk minimisation measures:
- **Routine**: 200 units/ml carton and pen designed to visually differentiate the product from 100 units/ml product:
  - Yellow warning box on carton containing the wording: “Use only in this pen, or severe overdose can result”.
  - strength of “200 units/ml” is written in a yellow box.
  - Background colour is dark grey instead of white as for the 100 units/ml product.

Additional: Patient Communication provided to all patients receiving their first prescription

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Identifying risk of medication error post-marketing

- Common sources of error in post-marketing use:
  - incorrect preparation, dilution or reconstitution
  - IV products given by IM or SC routes (or vice versa)
  - incorrect storage
  - mix-ups due to similarities in naming, packaging/presentation
  - confusion between multiple dose forms, or standard vs modified-release formulations
  - tablets/capsules not used as intended
  - children mistaking medicated gums and chewable tablets for sweets
  - incorrect use and disposal of transdermal patches
  - difficulty using drug-device combination products (e.g. poor inhaler technique)
  - confusion in use when switching from a familiar, established product to a new product
- **Capture in risk management plan** and describe what errors have been reported in post-marketing use, and how this has been addressed through changes in product design, labelling, packaging etc
- Consider/propose risk minimisation measures as appropriate – is describing in product information enough? How to communicate to HCPs/patients?

Medication errors – products with highest number of Yellow Card reports

Medicinal product	Number of reports
Clozaril	341
Zaponex	166
Mifegyne	99
Nicorette	77
Humira	75
Humalog	66
Implanon	65
Durogesic Dtrans	61
Paracetamol	49
Fentanyl	47

Examples of medication errors frequently reported post-marketing

Product	Reaction	# of reports
Durogesic Dtrans	Wrong technique in product usage process	30
	Inappropriate schedule of drug administration	16
	Accidental overdose	6
	Drug administration error	6
Humalog	Drug administration error	16
	Wrong drug administered	14
	Medication error	11
	Incorrect dose administered	10
Implanon	Incorrect drug administration duration	35
	Inappropriate schedule of drug administration	15
	Drug administration error	5
	Incorrect route of drug administration	3

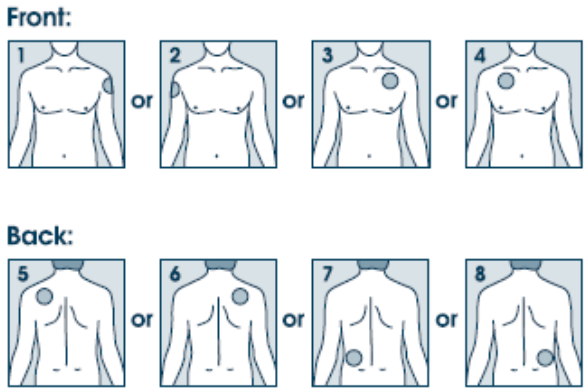
Case studies of ADRs relating to medication errors identified post-marketing – Implanon/Nexplanon

- Nexplanon indicated as long-acting reversible contraception
- Spontaneously-reported cases of insertion errors, difficulty removing device and device dislocation with earlier product, Implanon
- Risk minimisation:

- **Routine**: reformulated as Nexplanon, contains barium and can therefore be located on an X-ray or CT scan, new preloaded applicator, designed to reduce the risk of insertion errors
- **Routine**: product information updated to clarify instructions for insertion/removal
- **Additional**: Faculty of Sexual and Reproductive Health offer training on Nexplanon insertion (to obtain 'Letter of Competence in Subdermal Contraceptive Implant Techniques')
- Recent reports of Nexplanon being found rarely in vasculature, chest wall, and lung – advice on insertion and placement checking issued to HCPs in June 2016 via 'Drug Safety Update'

Case studies of ADRs relating to medication errors identified post-marketing – Exelon (rivastigmine) patches

- Exelon indicated in symptomatic treatment of mild to moderately severe Alzheimer's dementia.
- accidental overdoses of rivastigmine reported when patches applied for longer than recommended, at wrong site, when cut, or more than one patch applied
- Risk minimisation:
  - **Routine**: product information updated to clarify instructions for correct use
  - **Additional**: Direct Healthcare Professional Communication informed HCP of risk of medication error and reminded them of proper use and application of the patch
  - **Additional**: educational materials for patients developed which highlight how and where to apply patches, and include a medication record sheet



Old patch removed?	Date of application of new patch
✓	3 Oct 14

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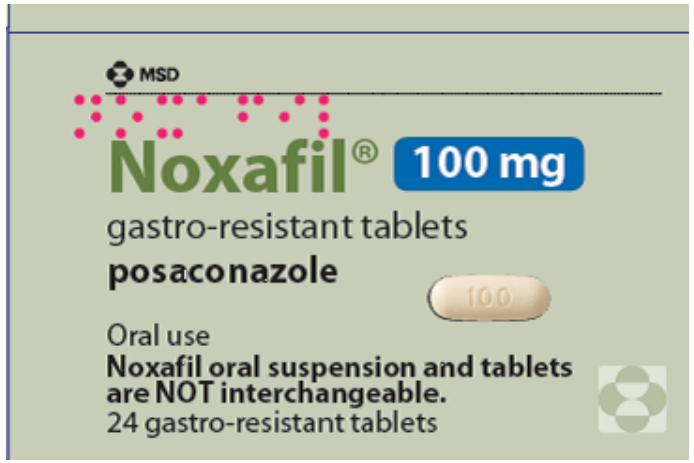
Case studies of ADRs relating to medication errors identified post-marketing – Noxafil (posaconazole)

- Noxafil indicated in treatment of fungal infections, available as 100mg oral tablet and 40 mg/ml oral suspension; recommended doses for the two forms are different
- Reports received of:
  - patients receiving oral solution instead of tablets, leading to underdosing
  - patients given tablets instead of oral solution, leading to overdosage
- Risk minimisation:



- **Routine**: existing warnings in SmPC and PIL strengthened, two forms not interchangeable, packaging updated to distinguish the two forms and carry warning that the tablets and oral solution are not interchageable
- **Additional**: Direct Healthcare Professional Communication informed HCP of the revisions to labelling, advised:
  - prescribers to make clear which form is intended for the patient
  - pharmacists should ensure that the correct form is dispensed

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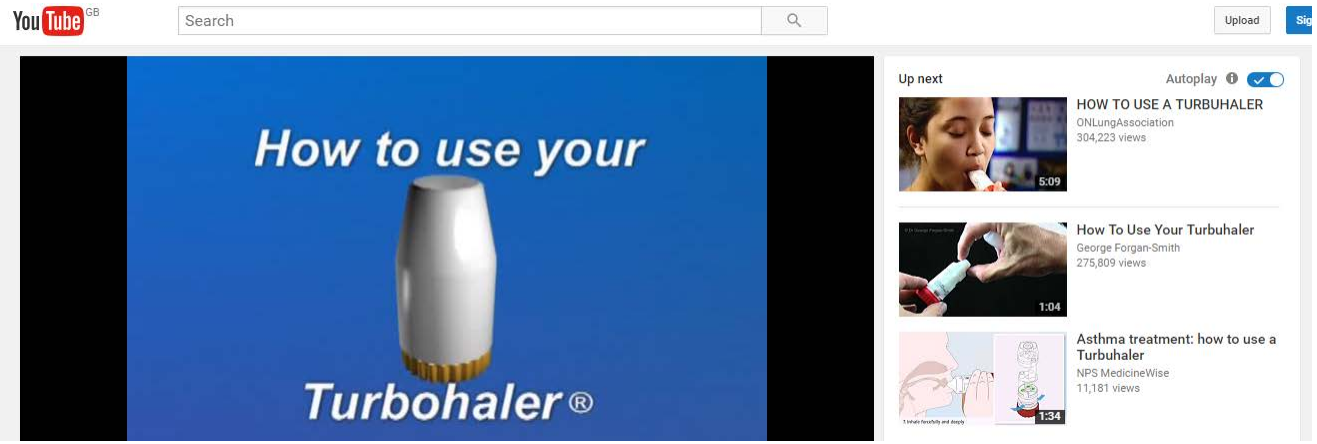
Risk minimisation tools – reaching the right audience

- Increasing use of the internet HCPs and patients to obtain information on medicines
- SmPC and PIL available on websites: EMA, national competent authorities, MAHs
- DHPC still sent in hard copy in most instances
- Educational materials:
  - agree with NCA whether active distribution necessary or not, agree method of distribution consider co-ordination with BGMA
  - Consider including patient materials in packaging – will reach all patients
- Other materials ('grey area') – non-promotional videos may be helpful



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Risk minimisation tools – reaching the right audience

- Limitations of electronic distribution:
  - Difficulty with hosting materials (only) on websites as a means of distribution is that users/prescribers do not know the materials exist, so do not know to look for them
  - Can be difficult to maintain up-to-date e-mail lists to alert all relevant recipients to the existence of materials (especially if going to all GPs)
  - E-mail to alert stakeholders to materials could be acceptable where:
    - company can demonstrate to NCA's satisfaction that their email distribution list was adequate (especially if data can be collected on number of e-mails opened and read)
    - issue affects only a small number of recipients/centres, where followup is more feasible than with larger-scale distribution
  - Materials may be hosted on non-promotional websites but hard copies should be made available on request

Summary

- SUMMARY
  - Medication errors may occur and be identified at all stages of product life-cycle:
    - During development
    - With changes to MA
    - In post-marketing use
  - Risk management plan should be used to capture potential medication errors and those which have been reported, and what measures have been put in place to minimise risk (as well as measuring impact!)
  - Consider which are best tools for risk minimisation and how these will reach the right audience
  - Ensure risk of medication error is communicated and that people are aware of any new advice or measures to minimise risk

Ask