Where incorrect dosing is likely to result in a potential serious risk to the health of children, measures such as a dedicated measuring device, application of unit-dose packaging or the selection of another dosage form should be considered.

The volume of the dose of an oral liquid preparation may have an impact on the patient acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation allows for better taste masking.

Oral suspensions

Critical product quality attributes to be considered for oral suspensions include physico-chemical characteristics of the suspension such as viscosity, potential for foaming, air entrapment, sedimentation and sticking of the suspended active substance to the primary container and to the measuring device. Where sedimentation cannot be avoided, easy re-suspension with moderate shaking is required to reduce the risk of insufficient shaking and dosing errors due to inhomogeneous distribution of the active substance.

The risks of under- and overdosing to the child as a result of inadequate shaking should be discussed. Clear instructions on correctly withdrawing the dose from the container should be included in the SmPC and PIL, including warnings if incorrect shaking may lead to over- or under-dosing. Adequate measures should be undertaken in cases where incorrect shaking will result in a potential serious risk to the child's health. Such measures may involve the application of unit dose packaging or the selection of a different dosage form.

Oral drops

Oral drops can provide a useful means to administer medicinal products in low doses or small volumes. The risk of counting the incorrect number of drops, and the accuracy and precision of the volume dispensed should be justified in relation to the criticality of the dose. In order to avoid counting errors, alternative measuring devices should be considered where the dose comprises more than 10 drops. Unless otherwise justified, oral drops will only be considered acceptable for paediatric medicines containing active substances with a wide therapeutic window.

The volume dispensed (i.e. drop size) will be determined by the design and physical characteristics of the dropper, the physical-chemical properties of the liquid and how the dropper is handled. Clear instructions should be included in the SmPC and PIL on the correct use of the dropper.

Effervescent, soluble and dispersible preparations

Effervescent, soluble and dispersible preparations are intended to be dissolved or dispersed in liquids prior to administration. The suitability of effervescent preparations for use in children may be restricted by the relatively large volume of liquid needed for dissolution and the high electrolyte content.

The minimum volume for dissolution or dispersion and any required rinse volume(s) should be discussed and justified in relation to the target age group(s). Clear instructions on how to prepare the solution or dispersion in a correct manner should be given in the SmPC and PIL. These instructions should include information on the minimum volume for dissolution or dispersion, including any rinse volume(s) and any specific requirements for stirring or mixing.

Similar to considerations for orodispersible and chewable preparations, the potential risks when administered without prior dispersion or dissolution should be considered. Any issues related to alternative modes of oral administration should be clearly stated in the SmPC and PIL.

6.2.3. Administration through feeding tubes

Oral medicinal products are likely to be administered via a feeding tube to patients who are tube fed due to their condition or age related limitations e.g. pre-term neonates, unable to swallow but able to receive enteral feeds.

Where administration through feeding tubes is used, either as a main route or as a very likely option, the feasibility of administration through the feeding tube needs to be addressed. The particle size, viscosity, dosing and rinse volume(s), chemical compatibility of the oral medicinal product with the tube material and the risk of physical blockage of the tube should be considered during pharmaceutical development. Dose recovery after extrusion needs to be demonstrated using feeding tubes and rinse volumes relevant to the target age group(s).

In addition, and if relevant depending on the location of the tube, the risks associated with the accidental aspiration of the medicinal product and the possible effect on the bioavailability should be discussed.

Where administration through feeding tubes is highly likely, the SmPC and PIL should provide information on whether the medicinal product can, or cannot be administered through a feeding tube, including instructions on the correct procedures.

6.2.4. Oromucosal preparations

The correct use and acceptability of oromucosal preparations will depend on the age of the child and the ability to keep the preparation in a specific part of the mouth over a defined period of time. The adhesive properties of oromucosal preparations should be discussed in relation to the local area where they should be applied. In order to avoid the risk of swallowing mouthwashes or dental gels, these dosage forms need to be applied in young children using a cotton bud, sponge or other suitable applicator.

6.3. Nasal preparations

Nasal preparations will normally be considered suitable for children of all ages. The suitability of the nasal route of administration for local and systemic treatment with a particular paediatric medicinal product should be discussed and justified in terms of the likelihood that the active substance (and excipients) will cause pain or irritation. The use of any preservative should be justified as outlined in section 9. The patient acceptability should also be discussed in relation to the palatability and sensation of the medicinal product on administration.

For nasal preparations with a local action, the risks of systemic (adverse) effects should be discussed. Devices for nasal administration, along with the intended delivered volume, should be suitable for the size of the nostrils/nasal cavity of the target age group(s).

6.4. Preparations for inhalation

The patient acceptability and age-appropriateness of orally inhaled paediatric medicines (including solutions for nebulisation) need to be justified.

Pressurized metered dose inhalers may be applied to children from birth if in combination with a specific spacer system and face mask. Older children may use the inhaler with or without a spacer. Companies should justify the suitability of the proposed equipment for use in the target age group(s).

Unless appropriately constructed, dry powder inhalers can only be used by older children because it is the child who activates the device by inhalation.

6.5. Rectal preparations

Suppositories

The size (length and diameter) of the suppository should take into account the age and size of the child. Due to the high risk of dosing errors related to inhomogeneous distribution of the active substance and difficulties in reproducible cutting, suppositories should not be cut to provide a smaller dose unless they have been specially designed for this purpose.

Liquid rectal preparations

The length of the rectal tube of the enema and any volume to be administered should take into account the age and size of the child. The use of scaled devices (pre-filled syringes with a rectal tip) should be considered where relevant. Clear instructions should be provided in the SmPC and PIL on the method for delivering the required dose to the child by the caregiver.

6.6. Cutaneous and transdermal preparations

Developmental changes in barrier function of the skin, such as dermis thickness, hydration and perfusion of the epidermis and the changing ratio of body surface area to weight, should be taken into consideration when developing cutaneous and transdermal paediatric preparations.

The use of excipients known to sensitize the skin (e.g. some surfactants and adhesives) should be carefully considered and justified. The need for or restriction from using water-impermeable or other types of materials as a coating to the cutaneous medicine should be clarified. Where relevant, the impact of occlusion, fever or thermal heating on skin permeability of the medicine and the consequent risk of overdosing should be discussed.

The size and shape of transdermal patches and medicated plasters should be tailored to the size and shape of the child body and should not interfere with daily routines. Application sites which cannot be easily reached by the child are preferred in order to prevent the child from removing the patch or medicated plaster. If sites reachable by the child are to be used, the impact of deliberate removal of the patch or medicated plaster on the clinical outcome should be discussed.

Patches and medicated plasters are preferably developed for use without the need for cutting to achieve a smaller dose, i.e. developed in a sufficient range of age-appropriate sizes or strengths. However, some types of patches (e.g. matrix types) may be developed to provide for a range of doses by cutting. Cutting will only be considered acceptable if clearly marked cutting lines are present and if the dose uniformity and consistency of delivery properties have been appropriately demonstrated.

Information on whether the patch can, or cannot be cut to provide a smaller dose needs to be included in the product information, with clear instructions on how lower doses can be obtained by cutting along marked lines. Instructions should also be provided for safely discarding the patch, and regarding the potential to use the remaining parts of the patch after cutting.

6.7. Eye and ear preparations

Preparations for the eye and ear are mostly developed for a single patient group, including children, adults and the elderly. Preparations for the eye and ear may be poorly accepted by some children.

However in the absence of better alternatives, they should be considered acceptable dosage forms for children of all ages.

In order to avoid the use of preservatives with a potential local toxicity to the cornea and/or mucous membranes, single dose preparations or multi-dose preparations in a dedicated multi-dose container that does not require its contents to be preserved, (i.e. preservative free containers), should be considered for children. This is especially important for neonates or if long term use may be necessary.

Young children can not yet be instructed to keep their eyes open. It is important that the parent is informed as to how to hold container and the child in order to correctly administer the medicine.

6.8. Parenteral administration

General considerations

Parenteral administration is the most commonly used route of administration for active substances for children who are seriously ill and for clinically unstable term and preterm neonates.

The choice of an intravenous, subcutaneous or intramuscular injection is to be justified in terms of the intended clinical effect, relevant characteristics of the active substance and child acceptance (pain).

The route of intravenous administration (central or peripheral), site of injection, the injection volumes, the rate of administration, the viscosity, pH, buffering, osmolarity and, if relevant, the needle thickness and needle length should be described and justified. The age and weight of the child, the maximum number of injections per day and the duration per treatment should also be discussed. Where appropriate, the use of micro-needles or needle free injectors could be considered, especially for medicines requiring frequent or long treatment period.

The need for serial dilutions to achieve the required dose is not acceptable as they are prone to errors and can be avoided by providing appropriate concentrations of the parenteral medicine.

The minimum dosing volume of a preparation will depend on the accuracy of the relevant measuring device. Where relevant, the size of the syringe and the graduation that permits accurate administration should be described in the dossier. The volume should be justified according to the age of the children in the target age group(s). Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml, however lower volumes are warranted for neonates and infants. Some parenteral preparations may be intended for emergency situations where venous access may not be easily established (e.g. resuscitation and intensive care). The suitability of medicines commonly used in such situations for use by the intra osseous route of administration should be discussed and relevant information should be provided in the SmPC and PIL.

Neonates may only accept very small volumes of medicines in order to avoid volume overload and to allow sufficient room for essential fluid nutrition. Infusions must not be so concentrated that the appropriate dosing rates are not feasible by using standard pump equipment. These aspects should be considered during pharmaceutical development of all parenteral preparations intended for neonates, and in particular of those intended to be administered as a continuous infusion. In addition, specific concerns related to the incompatibility of the medicinal product with other co-administered medicinal products in the infusion line, osmolarity, inappropriate diluents, and potential for over- or under-dosing due to lag-volume effects in *iv* fluid lines should be investigated.

Out-patient use

In cases where parenteral administration is required for children in out-patient settings, it should be demonstrated that the parenteral preparation is suitable for administration by the child itself or its

adult caregiver. This is especially important in cases where administration may also be necessary in situations where a trained caregiver is not present.

6.9. Fixed dose combinations

Fixed dose combinations are often developed as an alternative substitution therapy for patients already treated with the individual components, especially for chronic diseases such as HIV or tuberculosis. They may be of value for patients to simplify therapy and improve adherence. When clinically relevant, the applicant should make efforts to consider all possible options for developing an age-appropriate fixed dose combination for all or some target age group(s), unless such a development would be prevented by the complexity of doses required or by the lack of flexibility to ensure an adequate dose adjustment.

7. Dosing frequency

The choice of the dosing frequency should be justified in terms of the characteristics of the active substance, the pharmacokinetic profile, the indication, the convenience and therapeutic adherence of the child or caregiver. Taking these criteria into consideration, a maximum of twice daily dosing is preferred for out-patient use. For paediatric medicines that may be used more than twice daily, special attention should be given to the suitability of administration in out-patient settings where a trained caregiver is not readily available (kindergarten, school, etc.).

8. Modified release preparations

Modified release medicines should be considered for children where relevant. The development of modified release preparations should not be restricted to the oral route of administration. Alternative routes of administration could be applicable depending on the active substance characteristics (e.g. transdermal).

The use of prolonged release formulations can significantly reduce the dosing frequency and can be beneficial for compliance. Therefore these formulations can be useful for children who would otherwise need to take medication while at school or during the night.

For oral solid modified release preparations, the risk of chewing is to be considered when selecting this dosage form for further development. The risk of chewing and its impact on the efficacy and safety of the preparation should be discussed and it should not result in a serious risk to the health of the child.

In the development of oral modified-release preparations for paediatric use, special attention should be given to the physiological conditions related to the age of the child, e.g. gastric pH and gastro-intestinal motility (gastric emptying, transit time) and their variability since these characteristics could have an impact on the drug absorption.

9. Excipients in the formulation

9.1. General considerations

The choice of suitable excipients in a paediatric medicinal product is one of the key elements of its pharmaceutical development.

Although the basic considerations regarding the use of a specific excipient are similar for adult and paediatric preparations, the inclusion of any excipient in paediatric preparations, even those which are normally accepted for use in medicines for adults or those which are present in authorised paediatric

medicines, requires special safety considerations. The intake of an excipient may result in a different exposure in children to that in adults, or in children of different ages. Also the excipient may have a different effect on developing organ systems. A conservative approach should be followed in case of limited safety data relevant to the use of an excipient in a specific age group.

Overall, the following aspects are to be considered when selecting an appropriate excipient for inclusion in a paediatric medicinal product:

- the function of the excipient in the formulation and potential alternatives;
- the safety profile of the excipient for children in the target age group(s) on the basis of single and daily exposure (and not the concentration or strength of the preparation);
- the expected duration of the treatment i.e. short term (single dose/few days) versus long term (weeks, months, chronic);
- the severity of the condition to be treated (e.g. life-threatening disease) and the therapeutic alternatives;
- the patient acceptability including palatability (e.g. local pain, taste);
- allergies and sensitization.

In case the use of excipients with an identified risk cannot be avoided in the formulation of a particular pharmaceutical dosage form, the added value of the chosen pharmaceutical dosage form (and route of administration) should be well balanced against the possible use of other pharmaceutical dosage forms and routes of administration that do not require the use of such excipients. A comprehensive development rationale should be provided, taking into consideration the relative benefits and the risks of possible alternatives.

New evidence may suggest that there could be safety issues related to excipients used in authorised paediatric medicines, either as such, above a specific daily intake or for distinct target age group(s). In these cases, as a precautionary measure, applicants are recommended to avoid excipients with a potential cause for concern in newly developed paediatric medicines until further research allows scientifically justified conclusions on safety of these excipients to be drawn.

While it is acknowledged that the use of a novel excipient (i.e. an excipient used for the first time in a medicinal product or by a new route of administration) is fundamental to pharmaceutical innovation and that the use of such novel excipients may be well justified by appropriate pre-clinical studies, it must be realized that safety issues may only become apparent when the product is used on a larger scale. Therefore, the added value of the novel excipient in a specific paediatric medicinal product must be well balanced against the use of other excipients with an established safety profile, other dosage forms or other routes of administration.

Allergies can arise in early childhood and children may be more easily sensitized than adults. In order to avoid sensitization and to expand treatment possibilities of allergic children, applicants should consider avoiding, where possible, excipients with a known potential to cause sensitization or allergies.

The following information sources (listed in hierarchy) should be consulted in order to assess the safety profile of each excipient in a paediatric formulation (see Figure 1) resulting in an overall conclusion as to whether or not additional data are needed:

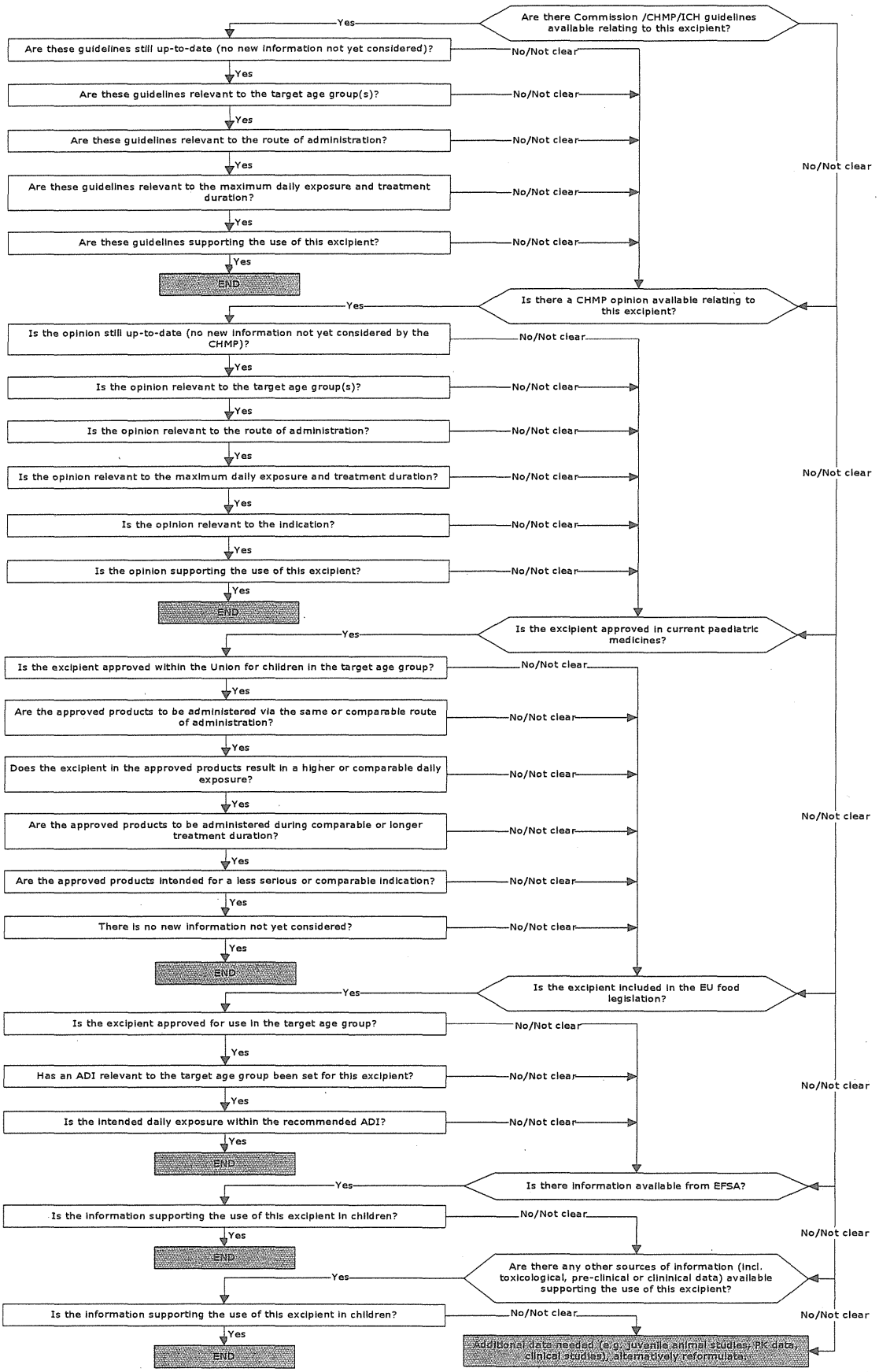
- Commission, ICH and EMA guidelines;
- CHMP scientific opinions (e.g. CHMP position paper, CHMP opinion on a referral procedure);

- Qualitative composition of an excipient in medicinal products currently authorised for use in children, and their quantitative composition if known;
- Food Legislation;
  - this source of information poses some limitations as it relates to food only (i.e. chronic and long term oral use);
  - all relevant excipients described in the Food Legislation as suitable for the paediatric population are normally considered acceptable for use in oral paediatric medicines unless there are additional safety indications from the other information sources and unless the wording in the Food Legislation itself causes reason for concern. In case of such additional concerns, the excipient should either be omitted from the formulation or the applicant should justify why the inclusion of the excipient can be considered acceptable;
  - the aforementioned does not apply to neonates for which further non-clinical data will normally be required;
  - the safety of relevant excipients described in the Food Legislation requires further evaluation for use in non-oral dosage forms.
- The European Food Safety Scientific Opinions (EFSA);
  - this source of information poses some limitations as it relates to food only (i.e. chronic and long term oral use) and the data may not relate to children. However a warning for adults should question the safety of the excipient for use in children.
- Other sources of information as e.g.;
  - expert committee on food additives (JECFA), which is a mixed committee of the WHO and the Food and Agricultural Organisation;
  - information in indexed literature;
  - in-house information as non-published scientific evidence.

The relevance of the acquired data for the excipient in the proposed paediatric preparation should be summarised and discussed in relation to the target age group(s), indication, route of administration and type of dosage form, treatment duration, maximum daily intake of the excipient and exposure.

It is emphasized that it is the responsibility of the applicant to justify that each excipient in a paediatric preparation is safe for its intended use in the target age group(s). Toxicological studies may be necessary if the use of an existing excipient in a paediatric medicine can not be justified on the basis of the aforementioned information sources.

Figure 1: Points for consideration in the evaluation of the safety profile of excipients in paediatiric formulations for a specific target age group



END = no further need to justify the use of the particular excipient in the paediatric medicine (when the excipient or the medicinal product meets the conditions stated)

9.2. Colouring agents

The use of any specific colouring agent in a paediatric preparation should be discussed and justified in terms of allergenic potential, minimal toxicological implications in the target age group(s), patient acceptability and the need to avoid accidental dosing errors. Where there is a need to differentiate between similar preparations to avoid accidental dosing errors, the use of other strategies e.g. shape, size and embossing should be considered prior to the use of colouring agents. The justification should address both the necessity to colour the preparation and the selection of a particular colouring agent.

Unlike other excipients, the use of colouring agents in medicinal products is governed by a specific directive (Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicines).

9.3. Flavours

Adequate palatability plays an important role in patient acceptability, especially in oral liquid formulations, and flavours may be necessary to achieve this goal. The rationale for the use of a particular flavour in a paediatric preparation should be clearly described and justified. The qualitative and quantitative composition of any components of the flavouring agent that are known to have a recognised action or effect should be provided. Safety concerns should be discussed, including the risk of allergies and sensitization.

9.4. Preservatives

The use of preservatives is normally considered acceptable in multidose preparations. However, for many preservatives there is still limited data regarding the levels of safe exposure in children of different ages. The need to preserve a paediatric preparation and the choice of the preservative system at the lowest concentration feasible should be justified in terms of benefit-risk balance.

The appropriateness of the preservative system for the target age group(s) should be discussed. Unless safety data relevant to children are available, applicants should justify the level of exposure (proposed safety margins) taking into consideration thresholds for adults and the possibility of alternative dosage forms.

Pharmaceutical companies are encouraged to consider novel strategies that allow the preservative-free formulation of paediatric medicines.

9.5. Sugars and sweeteners

Adequate patient acceptability of oral paediatric preparations is paramount and sweetness plays an important role in this.

The choice and concentration of sweetening agents depends on the properties of the active substance and the use of flavours. The rationale for the use of a particular sweetening agent in a paediatric preparation should be clearly described and justified. Safety concerns should be discussed, including conditions that would restrict the use of a particular sugar or sweetener (e.g. diabetes, severe renal insufficiency).

Frequent and/or high doses of sweetening agents should preferably be avoided in paediatric formulations intended for long term use. The use of cariogenic sugars should be carefully justified. The potential laxative effect of polyols (e.g. sorbitol, mannitol) should be considered, along with their osmotic properties and their potential effects on bioavailability. It should be noted that limited data are available on the relevant thresholds for polyols in children.

Alternative approaches to taste improvement (coating, complex formation, choice of vehicle, adjustment of viscosity) should be considered where relevant.

10. Patient acceptability

Patient acceptability is likely to have a significant impact on patient adherence and consequently, on the safety and efficacy of a medicinal product. Acceptability is determined by the characteristics of the product and the user. The product aspects relate to pharmaceutical characteristics such as:

- palatability, swallowability (e.g. size, shape, texture);
- appearance (e.g. colour, shape, embossing);
- complexity of the modification to be conducted by the child or its caregivers prior to administration;
- the required dose (e.g. the dosing volume, number of tablets, etc.);
- the required dosing frequency and duration of treatment;
- the selected administration device;
- the primary and secondary container closure system;
- the actual mode of administration to the child and any related pain or discomfort.

Evaluation of the patient acceptability of a paediatric preparation should be an integral part of the pharmaceutical and clinical development. Patient acceptability of a preparation should preferably be studied in children themselves as part of a clinical study involving the proposed medicinal product. In justified cases where no clinical studies will be conducted in children or where patient acceptability will not be studied as part of the paediatric clinical studies, adequate patient acceptability of the medicine(s) as proposed for marketing should be demonstrated by other means e.g. by literature references or by studies in dedicated adult panels.

For authorised medicinal products for which the acceptability of the preparation was tested and confirmed during the development or established by market experience, adequate patient acceptability should also be assured during the life-cycle of the product. In case of variation(s), which may have an effect on patient acceptability, e.g. changes to the composition of the authorised formulation, changes to the packaging or user instructions, etc. the impact of the change should be discussed and studied where appropriate and adequate patient acceptability should be reconfirmed.

Adequate patient acceptability is not to be understood as 100% acceptability of a medicine by children in the target age group(s). Moreover, different methods have been described in literature, which resulted in different outcomes when testing the same medicine in the same patient population. As knowledge on acceptability testing is still fragmented and an internationally harmonized method has not yet been developed, the choice of the method and the acceptance criteria are left to the applicant. However, the suitability of the chosen method to test the patient acceptability and the appropriateness of the applied limits should be discussed and justified in terms of benefit-risk considerations, including risks at population level (e.g. emergence of microbiological resistance due to poor acceptability of different preparations with antibiotics). The characteristics of the target age group(s), the condition relevant to the paediatric medicine, single or multiple use, the duration of treatment and any co-medication should also be considered.

Palatability

Palatability is one of the main elements of the patient acceptability of an oral paediatric medicinal product. It may also be an aspect related to the use of a product for nasal administration or inhalation. Palatability is defined as the overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e. feeling in the mouth). It is determined by the characteristics of the active substance, the way the active substance is formulated into a finished medicinal product and by the characteristics of the excipients. Information on the palatability of the active substance should consequently be acquired at an early stage in the development of a medicinal product, e.g. from dedicated adult panels or literature. The palatability of an active substance should contribute to the choice of the selected finished dosage form(s) and route(s) of administration. Unless otherwise justified, the palatability of a paediatric preparation should be satisfactory on its own merit, i.e. without mixing with food or drinks.

A paediatric preparation with a neutral taste or a paediatric preparation with a specific and generally acceptable taste may be developed. The choice of either of these profiles should be justified. Normally, development of medicinal products with a neutral taste should be considered, especially for medicines used in the treatment of chronic conditions, as strong flavours can become unpalatable with repeated administration. The development of a formulation with the intended target palatability (neutral or a specific taste) should be clearly described and justified.

Examples of measures that can be undertaken to improve the palatability of a paediatric preparation include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), a change in particle size of the active substance or the excipients, a choice of a different salt of the active moiety, coating of the active substance, coating of the finished dosage form, use of a complexing agent (e.g. cyclodextrines) or for liquid preparations, lowering the amount of the free active ingredient in solution by the choice of a different strength and associated change in volume. However, paediatric preparations must not become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning.

Mixing with food or drinks

For a variety of reasons, it may be desirable to give a paediatric medicine with food or drinks. Mixing with food or drinks may either be intended to mask the unsatisfactory palatability of a formulation in cases where it has been demonstrated that it cannot be further improved or where alternative dosage forms cannot be developed. Mixing can also be applied as a further means to improve the patient acceptability including the ease of swallowing of an otherwise already palatable medicinal product. Whatever the reason, the rationale should be discussed and justified in the dossier, and relevant information included in the SmPC and PIL.

The absence of recommendations on mixing with food or drinks will not assure that caregivers will not employ this method in order to administer a medicinal product. Therefore, the effect of mixing the product with common food or drinks as specified by the applicant should be discussed for every oral paediatric medicinal product.

Different food or drinks may have different properties and differ in their effect on the paediatric preparation. The applicant's choice of food or drink should be justified in terms of their actual effects on the properties of the preparation (e.g. acceptability, compatibility and stability). It is understood that food and drinks are usually not standardized products and that the whole range of variability cannot be verified by e.g. acceptability and compatibility studies. Nevertheless, the SmPC and PIL should give clear instructions on what food and/or drinks, if any, have been demonstrated to be appropriate for mixing with the paediatric preparation. If mixing with food or drinks has been evaluated and found to be unsuitable, appropriate warnings should be provided in the SmPC and PIL,

along with an explanation of the basis for such warning. If mixing with food or drinks has not been studied, this should also be stated in the SmPC and PIL. In all cases it should be stated that any mixing outside the recommendations is the responsibility of the health care professional or the user.

The user should be instructed that, in order to facilitate administration of the whole dose, the medicinal product should be mixed with a small portion (e.g. one spoon) or otherwise justified quantity of the food or drinks, and needs to be taken within a clearly specified time period after mixing. In exceptional cases a larger quantity may be necessary to assure adequate palatability or dissolution. Large amounts of food or drinks (e.g. one full cup, glass or meal) should be avoided because of the risk that the child may not be able or willing to take the full quantity and consequently will not receive the full intended dose of the medicine. If chewing of the product is expected to affect the acceptability and/or product performance, the SmPC and PIL should clearly state that chewing after mixing with food or drinks must be avoided.

Unless otherwise justified, compatibility should be demonstrated by appropriate studies. The time period during which the mixed product remains acceptable, should be indicated in the SmPC and PIL including information on any restrictions on the temperature of the food or drinks.

Mixing with food or drinks may affect the product performance and the pharmacokinetic behaviour. When mixing with food and/or drinks is proposed, the possible effect on biopharmaceutical characteristics of the medicinal product should be discussed. Assessment of the impact on bioavailability of products mixed with food or drinks may be needed depending on information that is available from studies undertaken during the development of the product, including studies in adults, if relevant to the paediatric medicine.

If the product has been administered following mixing with food or drinks in the clinical trials, no further evaluation may be needed. Mixing with food or drinks is generally discouraged for medicines containing substances with a narrow therapeutic window.

11. Container closure system, measuring device, administration device and packaging

11.1. General considerations

The container closure system and administration device should be designed for use in the target age group(s). When used together, they should allow the appropriate use of the medicine.

Unless otherwise justified, container closure systems for use in adolescent children should be discrete and portable and, where reasonable, enable individual doses to be taken to school, sports, etc. Where relevant, the SmPC and PIL should state that the medicinal product should only be used in combination with a designated administration device.

Applicants are encouraged to consider novel packaging and administration strategies that improve child acceptability, child adherence and child caregiver convenience while reducing the risk of accidental dosing errors.

The container closure system should differentiate the medicinal product from confectionary and toys to reduce the attractiveness of the product to children.

The practicality of the container closure system and administration device should be considered. For example, some bottles used for oral liquid medicines are small enough to allow removal of the entire contents with an oral syringe of appropriate length. Other containers will require a "syringe adaptor",

which is an integrated bung in the neck of the bottle into which the oral syringe fits. The syringe adaptor allows successfully remove the entire contents of the container.

11.2. Container size

General considerations

The full contents of a container should be justified in terms of:

1) dosing recommendations and dosing duration in the SmPC and PIL for each of the target age group(s);

2) accidental dosing errors, specially the risk of 10-fold overdosing;

3) accidental ingestion of the full contents;

4) patient acceptability.

11.3. Measuring device

Specific attention should be given to the ease and accuracy of the administration. The criticality of the dose i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window should also be discussed.

Unless otherwise justified liquid paediatric medicines should be supplied with a measuring device. The physical characteristics of the liquid preparation in relation to the measuring device will play a part in determining the accuracy of dosing. The combination of the paediatric preparation and the measuring device should be investigated in order to ensure accurate dosing.

There may be situations where it is claimed that it is not necessary to supply a measuring device with a paediatric medicine. In these cases it should be demonstrated that accurate dosing is achieved with a range of commonly available measuring devices such as measuring spoons and measuring cups. The user instructions should be specific to the type of measuring device(s) to be employed.

The age appropriateness of an administration device should be discussed. For example, an oral syringe may provide a more reliable method of administration for oral liquids in the youngest age groups than a spoon or a cup.

The nominal volume of the measuring device and the graduation on the device should be assessed in view of the recommended doses, the risk of over and under dosing and the availability of multiple strengths of the medicinal product. Measuring devices may be used for repeated oral dosing, if appropriately cleaned. A cleaning instruction should be included in the SmPC and PIL.

If a device is specifically designed to deliver the correct doses for a particular medicine, e.g. a cup to measure a particular number of granules, then the product name should be displayed on the device in order to avoid the accidental use of measuring devices for different medicinal products.

Some measuring devices such as oral syringes may contain some dead space. The significance of the dead space increases as the volume measured decreases. Therefore this issue needs to be discussed. It should be demonstrated that the dead space is insignificant to the dosing accuracy when the minimum intended volume is measured. Incorrect flushing of syringes and needles may result in a relevant overdose of the intended volume for administration. The risk of such overdosing to the health of the child should be discussed. In relevant cases, an appropriate warning i.e. not to flush the syringe and needle may be considered in the SmPC and PIL.

The accuracy of measuring devices for paediatric medicines with a steep dose/pharmacodynamic response curve or narrow therapeutic window may require special considerations.

11.4. Other devices

For routes of administration requiring the use of a specific administration device, the appropriateness of the device for the target age group(s) should be justified, e.g. face masks, nebulisers.

Aspects to be discussed include the ease of administration by the child or its caregiver, difficulties in administration to unwilling children, and the robustness of the device in daily practice. Any necessary device should be dispensed with the product unless the applicant can demonstrate that the device is commercially available.

12. User information (summary of product characteristics and package leaflet)

Applicants should provide clear user instructions that favour the correct and full administration of a paediatric medicine. These instructions should take account of the different administration scenarios to children from birth into adulthood. Where relevant, instructions that are both suitable for the caregiver as well as the child are strongly recommended. User instructions should be sufficiently robust towards unwilling children, especially where full adherence is critical for therapeutic outcomes.

Detailed instructions can be found in the guideline on the SmPC.

Definitions

Age-appropriate paediatric medicine

A medicine, whose pharmaceutical design makes it suitable for use in the target age group(s).

Modification

All activities prior to administration that are undertaken in order to provide the medicine to the patient using an alternative strategy (e.g. in order to improve patient acceptability or adjust the dose). Information on verified modifications (approved by the regulatory authority) should be described in the SmPC and PIL. Non-verified modifications if undertaken off-label are under full responsibility of the health care professional or the user.

Paediatric formulation

The composition of a particular dosage form of a medicine for paediatric use.

Paediatric medicine / paediatric medicinal product

A paediatric preparation in its container closure system, together with any measuring and administration device and the user instruction.

Paediatric preparation

A paediatric formulation in a particular strength (e.g. tablets 5 mg, solution for injections 5 mg/ml) and, in case of paediatric formulations for single use, the labelled container contents (e.g. solution for injection 5 mg/ml, 1 ml = 5 mg or 2 ml = 10 mg).

Patient acceptability

The overall ability and willingness of the patient to use and its care giver to administer the medicine as intended.

Pharmaceutical design of a medicine

The composition, dosage form, route of administration, dosing frequency, packaging, measuring or administration device and the user instruction of a medicine.

Pharmaceutical development

In the context of this guideline, pharmaceutical development relates to all aspects as described in module 3.2.P of the common technical document, the user instruction in the SmPC (section 6.0) and the PIL. It is defined as the process of turning an active pharmaceutical moiety into a paediatric medicine that is suitable for administration by the child itself or its adult caregiver, including all related pharmaceutical aspects as e.g. the control of raw materials, the validation of analytical methods etc.

Preliminary preparation (as called enabling preparation)

A relatively simple and easy to prepare formulation that facilitates the preclinical and/or early clinical development studies which might otherwise be delayed whilst developing the final age-appropriate paediatric medicine.

Verification (of a modification)

A process of providing any type of adequate evidence, e.g. new (bio)analytical data, from the literature or by referencing to existing practices to support that the proposed modification will not change the pharmaceutical characteristics of the original preparation in a way that it will negatively impact the safety and/or efficacy of the medicine.

資料2

汎用されるため錠剤・カプセル剤を粉砕して予製剤を行っている
小児用剤形として散剤開発が希望される医薬品例

（国立成育医療研究センター　2009年10月から2013年10月調査）

一般名	商品名	分類	現状の剤形
ダントロレンナトリウム水和物	ダントリウムcp	痙性麻酔緩解剤・悪性症候群治療剤	カプセル、静注用
アムロジピンベシル酸塩	ノルバスク錠	高血圧症・狭心症治療薬	錠剤、OD錠
オキシブチニン塩酸塩	ポラキス錠	尿失禁・尿意切迫感・頻尿治療剤	錠剤
プロプラノロール塩酸塩	インデラル錠	高血圧・狭心症・不整脈・片頭痛	錠剤、カプセル、静注用
プラゾシン塩酸塩	ミニプレス錠	高血圧症・排尿障害治療剤	錠剤
カルベジロール	アーチスト錠	高血圧・狭心症治療剤・慢性心不全治療剤	錠剤
バクロフェン	ギャバロン錠	抗痙縮剤	錠剤、髄注
グリチルリチン酸1アンモニウム・グリシン・DLメチオニン	グリチロン錠	肝臓疾患用剤・アレルギー用薬	錠剤
ヒドロコルチゾン	コートリル錠	副腎皮質ホルモン剤	錠剤
リシノプリル	ロンゲス錠	アンジオテンシン変換酵素阻害剤	錠剤
ラメルテオン	ロゼレム錠	メラトニン受容体アゴニスト	錠剤

錠剤・カプセル剤の粉砕量は少量だが小児用剤形として散剤開発が希望される医薬品例

シルデナフィルクエン酸	レバチオ錠	ホスホジエステラーゼ5阻害薬	錠剤
ボセンタン水和物	トラクリア錠	エンドセリン受容体拮抗薬	錠剤
ランソプラゾール	タケプロンcp	プロトンポンプインヒビター	カプセル、OD錠、静注用

国立成育医療研究センターで汎用のため錠剤・カプセル剤を粉砕して予製剤を行い
小児用剤形として散剤が希望される医薬品例

（2009年から2013年）

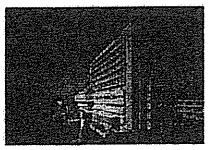
商品名	一般名	分類	現状の剤形
ダントリウム	ダントロレンナトリウム水和物	痙性麻酔緩解剤・ 悪性症候群治療剤	カプセル、静注用
ノルバスク	アムロジピンベシル酸	高血圧症・狭心症治療薬	錠剤、OD錠
ポラキス	オキシブチニン塩酸塩	尿失禁・尿意切迫感・頻尿治療剤	錠剤
ミニプレス	プラゾシン塩酸塩	高血圧症・排尿障害治療剤	錠剤
アーチスト	カルベジロール	高血圧・狭心症治療剤・ 慢性心不全治療剤	錠剤
ギャバロン	バクロフェン	抗痙縮剤	錠剤、髄注
グリチロン	グリチルリチン酸-アンモニウム・ グリシン・DLメチオニン	肝臓疾患用剤・アレルギー用薬	錠剤、皮下注
コートリル	ヒドロコルチゾン	副腎皮質ホルモン剤	錠剤
ロンゲス	リシノプリル	アンジオテンシン変換酵素阻害剤	錠剤
ロゼレム	ラメルテオン	メラトニン受容体アゴニスト	錠剤

錠剤・カプセル剤の粉砕量は少量だが小児用剤形として散剤が希望される医薬品例

レバチオ	シルデナフィルクエン酸	ホスホジエステラーゼ5阻害薬	錠剤
トラクリア	ボセンタン水和物	エンドセリン受容体拮抗薬	錠剤
タケプロン	ランソプラゾール	プロトンポンプインヒビター	カプセル、OD錠、 静注用

第34回日本臨床薬理学会学術総会
シンポジウム31-1
小児の薬と臨床薬理学・臨床薬学のこれから

小児に望まれる飲みやすい薬とは（剤形、味と飲みやすさから）



平成25年12月6日
国立成育医療研究センター
石川洋一

優れた薬効でもジスロマックDSは外来看護師に好まれない？

- マクロライド系抗菌薬は苦い
- 例えば、アジスロマイシンの製剤ジスロマックドライシロップは1日1回服用の画期的製品だが、その苦さで子どもが吐いてしまう
- 医療・薬理学的に最高の薬でも服用しない薬は効かないと言う問題にぶつかる
- 平成25年12月にジェネリックでアジスロマイシンが発売されるが、これは味が良い
- 小児用製剤にはこんな問題がある

世界中で小児用剤形が不足

- 小児用剤形が不足しているのは日本だけではない
- この事態を改善するには、臨床薬理学・臨床薬学を学んだ専門家のAdvocacyが必要
- 多くの識者の参画を望みたい

小児科領域における剤形変更の現状

平成17年度厚生労働科学研究
「小児薬物療法におけるデータネットワークの実用性と応用可能性における研究」

調査対象 ： 製品本来の剤形から投与剤形を変更し、使用した全医薬品
調査協力施設 ： 小児薬物療法ネットワーク研究協力施設　32施設

剤形変更して作られた剤形	医薬品の種類（規格違いを含む）	全体に占める割合
散　剤（粉砕・倍散等）	1227品目	74%
錠　剤（半錠・1/4錠等）	176品目	11%
水　剤（注射剤から調製等）	50品目	3%
坐　剤（分割）	40品目	2%
吸入剤（注射剤から調製等）	23品目	1%
その他	150品目	
合計	1666品目	

剤形変更上位10品目（調剤件数）

順位	一般名	医薬品名	薬効	調剤件数
1	ワルファリンカリウム	ワーファリン錠	血液凝固阻止剤	1052
2	メチルジゴキシン	ラニラピッド錠	強心剤	568
3	マレイン酸エナラプリル	レニベース錠	血圧降下剤	550
4	ダントロレンナトリウム	ダントリウムカプセル	骨格筋弛緩剤	482
5	リシノプリル	ロンゲス錠	血圧降下剤	456
6	ベラプロストナトリウム	ドルナー錠	その他の血液・体液用剤	444
7	ヒドロコルチゾン	コートリル錠	副腎ホルモン剤	406
8	バクロフェン	リオレサール錠	その他の中枢神経系用薬	374
9	抱水クロラール	抱水クロラール	催眠鎮静剤・抗不安剤	364
10	塩酸プロプラノロール	インデラル錠	不整脈用剤	356

平成17年度

なぜ小児用剤形が無いのか

- 薬物療法の臨床研究は成人が基本
- 治験を実施して適応を取得するのは基本的に成人適応
- したがって発売されるのは成人用の医薬品

なぜ小児用剤形が無いのか

- しかし、小児の臨床試験実施は少ない
- したがって成人の医薬品に小児適応は無い
- したがって小児用の剤形は開発できない
- しかし、小児にも治療薬が必要

日本では小児が使う剤形が無い

- では、小児用剤形の不足にはどのように対応し、改善するか

1）製薬企業による小児用製剤の開発促進
– どのような剤形が求められているかの情報が必要
2）薬剤師による剤形変更
– 法的な支援、安全確保のための情報作成と標準化促進が求められる

1）製薬企業への情報

- 医薬品によって物理化学的に不安定なものは、薬剤師は対応できない
- 湿度・光・周りに強く着色する
- 薬物動態が不明瞭
- 小児が服用する剤形は錠剤か散剤かシロップか、新しい剤形か
- どれだけの患児が国内にいるのか

WHOによる小児用剤形の開発推進

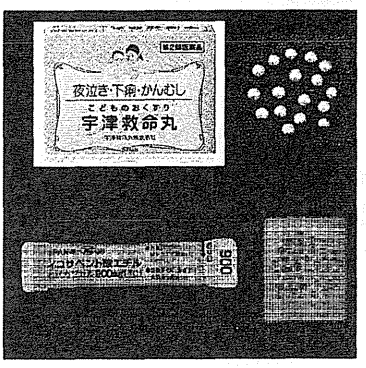
World Health Organization

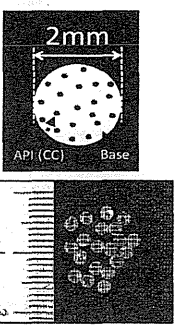
- Launched on 6 December 2007, 'make medicines child size' is a global campaign spearheaded by WHO:
  世界的に求められている小児用の剤形
- 服薬できなければ、薬としての効果は無い
- 我慢して飲めというのは正しくない
- 薬剤師の職能でも味や吸収、遮光等の物性には対応できない

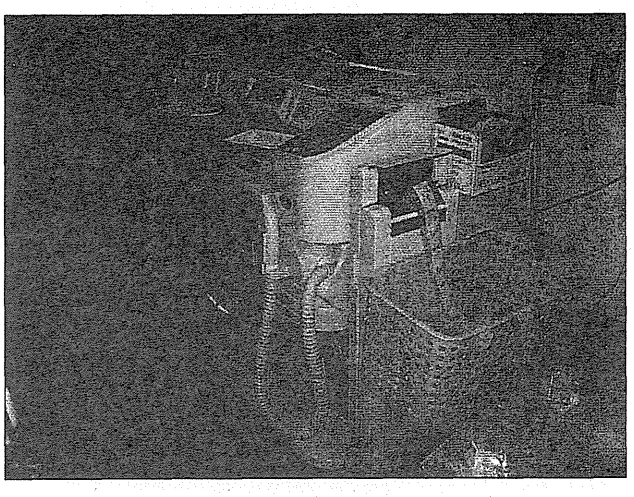
小児用剤形は散剤か錠剤か

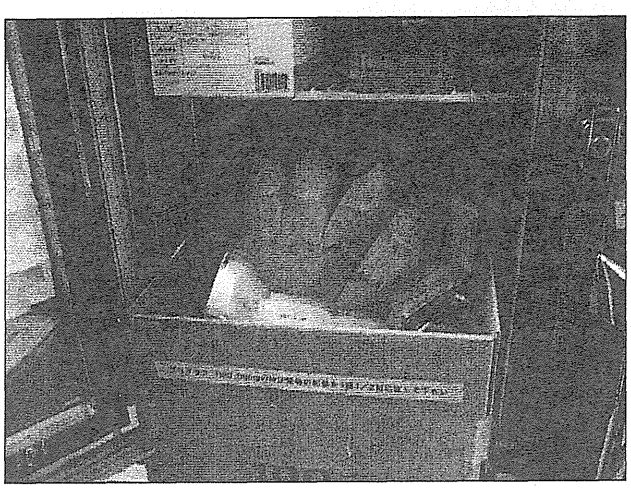
- 海外と異なり日本では散剤を服薬する習慣と技術がある
- 海外には散剤を分包して服薬させる技術がない
- 海外ではシロップ、懸濁剤に加えミニタブレットも小児用剤形改善の糸口と考えている
- 日本では過去から宇津救命丸と言うミニタブレット技術がある

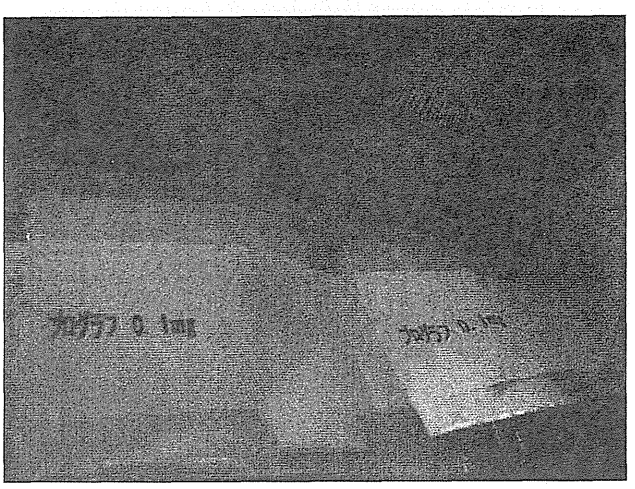
服用しやすい小児用剤形の研究

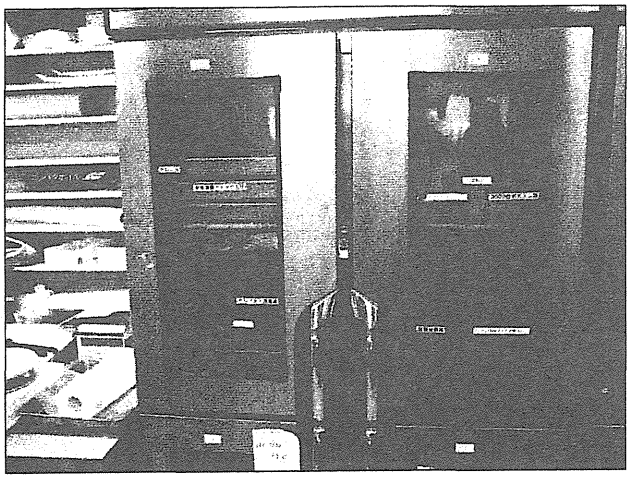


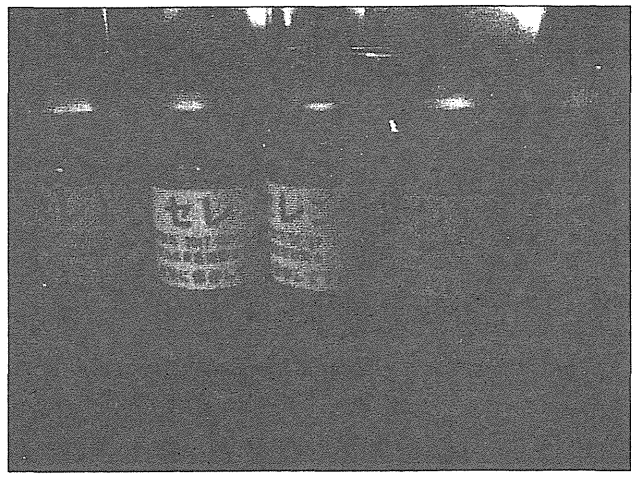












2）薬剤師への情報

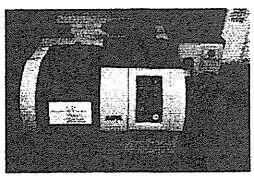
- 錠剤を粉砕した時の物理化学的安定性
- 医薬品としての薬物動態の変化
- 調剤への影響
- 倫理委員会での審議にはエビデンスとなる十分なデータが必要

適正な剤形変更に向けた研究の例 ワルファリンKの光安定性

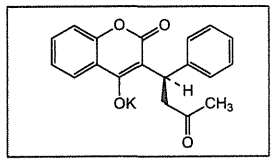
- 吸湿性への注意と同時に、光安定性が低いことに注意
- 原末から倍散にすると、光安定性がさらに低くなる
- 成育で1mg/g（0.1%）散を調整していた時は光被ばくで2週間で75%含量に落ち込む
  （照度：1000lx　シャーレ内データ）
- 遮光袋による提供が必要

適正な剤形変更に向けた研究の例 ワルファリンKの光安定性

Near-infrared (NIR) spectroscopy



FT-NIR spectrometer
(MPA, Bruker Optics K. K.)

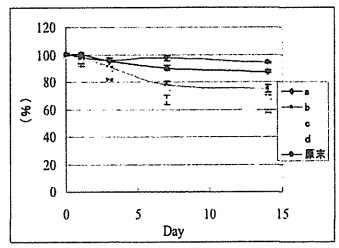


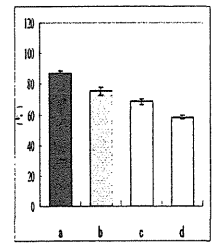
Structure of warfarin potassium
(Eisai Co., Ltd.)

（武蔵野大学 薬学研究所　大塚　誠、馬場本　絵未）

適正な剤形変更に向けた研究の例 ワルファリンKの光安定性

- 4社（先発、後発）比較で、それぞれ光安定性が異なることも明らかになった





Variation of warfarin potassium content after 14 day (mean values±SD)
(two-tailed Welch's *t* test, *$p<0.05$, **$p<0.01$)

**2011年12月改訂（第3版）
*2011年11月改訂

経口抗凝固剤

ワーファリン顆粒0.2%　Warfarin

（ワルファリンカリウム製剤）

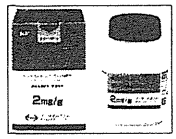
処方せん医薬品

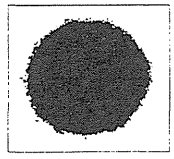
薬価収載	2011年12月
販売開始	2011年12月

2011年11月30日 エーザイ株式会社 プレスリリース

経口抗凝固剤「ワーファリン顆粒0．2%」日本で新発売

このたび新発売する「ワーファリン顆粒0.2%」は、嚥下困難や小児など錠剤の服用が困難な患者様に対して使用可能であり、微量調節もできる製剤となっています。本剤は、成分であるワルファリンカリウムを精密に0.5mg以下の微量に調節することを可能にするとともに、服用ボリュームの適量を確保するため500倍散に設定しています。また、ワルファリンカリウムは光によって分解していく性質を持っていますが、本剤は、顆粒をコーティングするなどの工夫を行うことにより、光安定性を高めた製剤となっています。





3）小児が飲めるかの情報

- 味・におい・ざらつきなど、成人では想定しない問題がある
- Palatability：患児に飲みやすいと評価される医薬品とはどんなものかはまだ研究不足
- 小児がどのような味を好みどんな苦さが嫌いかなどはまだ研究されていない
- 味覚センサーは、まだ小児の微妙なニュアンスはとらえられない