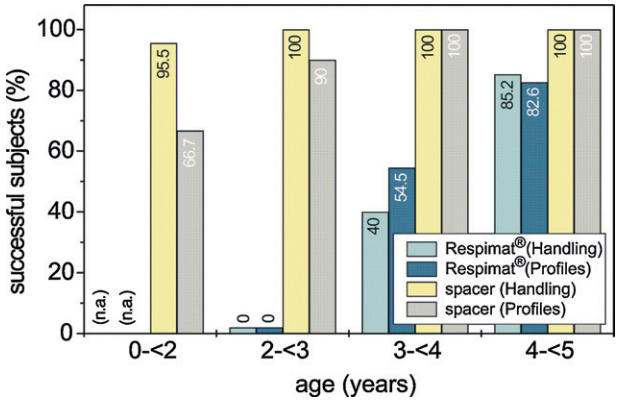

Fig. 2. Example of a handling study checking an inhaler with and without an accessory device. The percentage of successful subjects according to handling assessment or via air flow profile analysis is given, criterion = volume inhaled (acceptance level 0.15 L). Respimat® inhaler alone (with or w/o help by parents) compared to Respimat® inhaler with spacer (Kamin et al., 2011).

ation. Devices intended for children should also take into account the role of parents/caregivers.

An example of a clinical handling study has recently been included in a PIP. This handling study profiles the Respimat® Soft Mist™ Inhaler (RMT) which is an innovative, active, mechanically acting multi-dose aerosol generator. Being an active device, it is in Class IIb, as are e.g. special nebulizers. Its spray duration is approximately 1.5 s and therefore the spray takes longer than that of pMDIs (Hochrainer et al., 2005). So far the RMT inhaler filled with Tiotropium has been authorized in the indication COPD in the age group > 18 years (adults). A first handling study has investigated children from 4 to 12 years of age, recommending the use of Respimat from the age of 5 and older (Krackhardt et al., 2007). In the PIP, it was agreed to perform a "Handling study to assess the use of the device in children below 5 years of age". An age-dependent study design was chosen, taking into account possible assistance by caregivers e.g. parents and further simplification by an accessory spacer, the AeroChamber® Plus with face mask manufactured by Trudell Medical (Trudell, 2008). 99 subjects were included in the study. The study relied on a standardized assessment by trained medical personnel and on air flow profiles acquired during simulated administration. The result was, "to ensure standardized dosing, the use of the Respimat® inhaler with spacer (AeroChamber® Plus) is recommended for all children below 5 years of age" (Kamin et al., 2011). Fig. 2 shows the details of the investigation.

The combination of facemask, spacer, and inhaler can be used starting at a very young age and the inhaler itself is successfully applied beginning from 3 to <4 years of age. As successful handling is a prerequisite for consistent dosing, this study helps to avoid the use of conventional clinical studies just for the check of devices (von Berg et al., 2004). The result may justify the age range recommended in the instructions for use.

In summary, in the complex regulatory situation of a PIP, handling studies help to establish a first objective evaluation of the intended treatment at an excellent benefit/risk ratio for the paediatric population.

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Development of child-appropriate devices

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It is well known that the use of household spoons for dosing of liquid pharmaceuticals frequently results in high dosing deviations (Aziz and Jameela, 1990; Madlon-Kay and Mosch, 2000). Due to these reasons, liquid pharmaceuticals nowadays are often delivered with administering devices exhibiting a kind of scale for facilitated dosing, such as measuring spoons, dosing cups, oral syringes, or droppers. Nevertheless, dosing of liquid medicaments with such devices is yet far beyond accurate in many cases (Sobhani et al., 2008; Walsh et al., 2011 and references therein). For instance, Grießmann et al. (2007) reported significant dosing failures when the measuring devices supplied with commercial amoxicillin and erythromycin preparations were used.

Surface tension and viscosity of the medicament, visibility and size of the scales, kind of the employed dosing device, and also the individual opinion of the administering user affect the correct dosing. While those dosing variances may be neglected for adults, they are of significant importance for children since they require far less amounts of a medicament in comparison to adults. Hence, even small dosing deviations can have a high impact on the absolute administered dose. Furthermore, the required amount of a medicament directly depends on the size and the age of a child. An additional concern in paediatric administering of pharmaceuticals is to overcome the child's resistance taking the medicine. Reluctance is particularly pronounced when the medicament exhibits a disadvantageous taste.

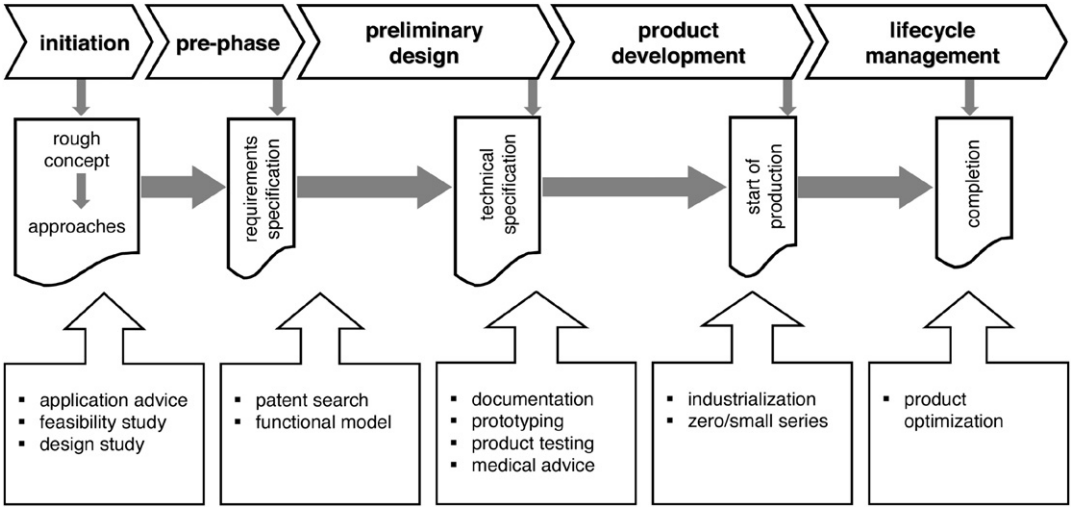

Fig. 1. Detailed scheme of a typical development process.

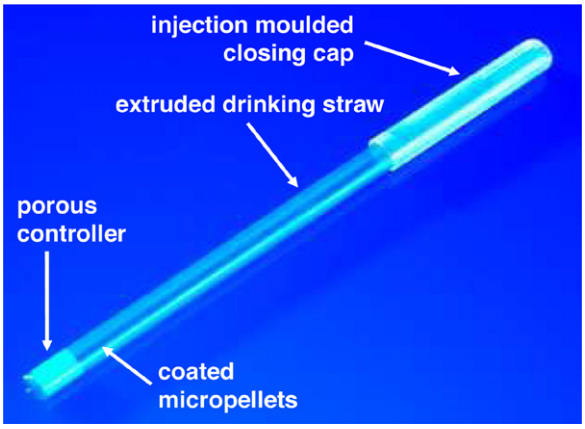

Fig. 2. Drug delivery device for pharmaceutical granulates, which is used like a drinking straw.

Since RAUMEDIC is highly aware of the mentioned issues, we developed – initiated by requests of our customers – a new class of paediatric administering devices. In each case, the cooperation was started at the very beginning with a rough concept and yielded in market-ready, child-appropriate dosing devices, which unite dosing accuracy and compliance adherence. The undertaken and typical development process in detail is shown in Fig. 1.

For the company Grünenthal we developed an oral drug delivery device, which basic principle is a drinking straw filled with a pre-defined amount of pharmaceutical granulates (Sternberger et al., 2010; Fig. 2). For drug administration, the child chooses its favourite drink and simply sips the drug pre-filled in a straw while upon swallowing the pharmaceutical starts to dissolve.

The easy handling like a straw provides a lot of fun and thus makes this device particularly suitable for children above the age of three. Furthermore, no dosing failure may occur because a single dose was pre-filled into the straw system. Additionally, this device allows the application for different pharmaceuticals by utilizing different straw colours, optionally combined with printed labels.

The idea of a straw employed as drug delivery device was then taken up by the company SANDOZ. But instead of packing solid granulates, the accurate, repeated and reproducible dosing of liquid medicaments was required. After great efforts and ingenuity, eventually a syringe, which also can be used as a drinking straw, met all those requirements (Schwarz et al., 2008; Jakob and Skaper, 2010).

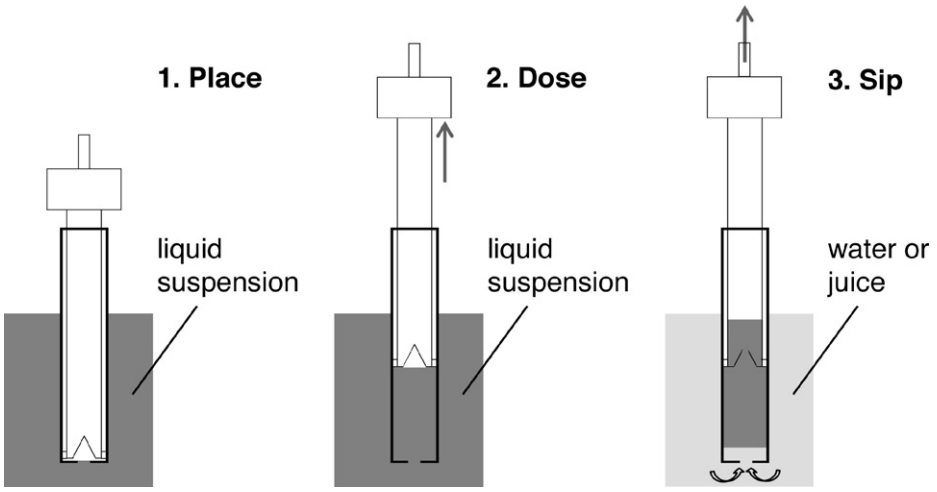

Fig. 3. Procedure of the dose sipping syringe application. First the syringe is placed in contact to a pharmaceutical liquid suspension (left). Then the pharmaceutical is dosed into the dose sipping syringe by pulling the piston (middle). Subsequently, the dose sipping syringe is placed into a glass of favoured drink, e.g. water or juice, and the medicament is taken by sipping at the mouthpiece on top of the piston (right).

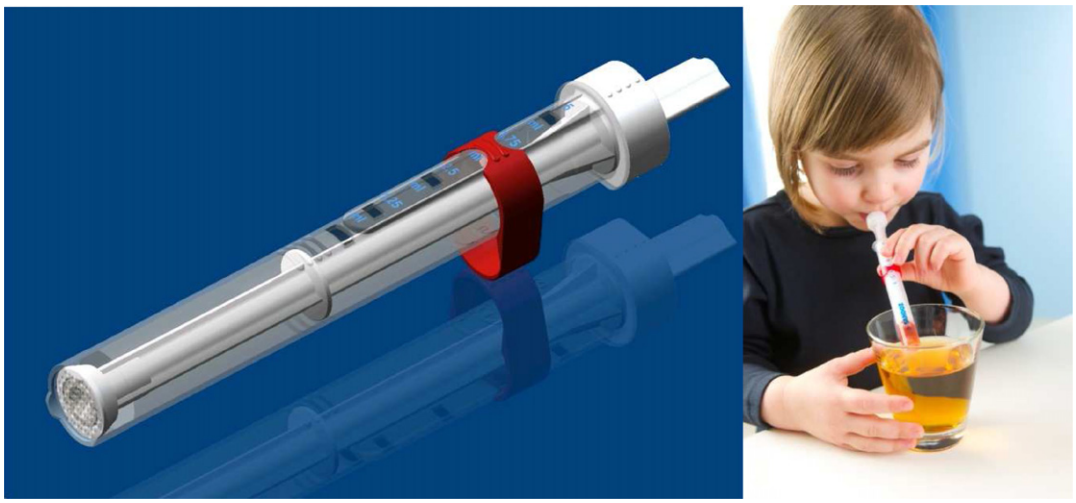

Fig. 4. Dose sipping syringe design (left) and child taking its medicine with the dose sipping syringe (right).

Having adjusted the prescribed dose with the surrounding plastic ring, the syringe is then filled by placing it into the liquid pharmaceutical and pulling the piston (Fig. 3). Alternatively, an adapter may be used which fits both to the syringe and the medicine bottle (Jakob et al., 2011). Then the pre-filled syringe is placed into a glass of liquid and the child may sip its favourable drink through the sipping device (Fig. 4). Doing so, a laminar flow assures complete uptake of the pharmaceutical while an unpleasant taste is suppressed by the floating drink.

Besides the safe and easy handling the dose sipping syringe assures dosing accuracy. Furthermore, the patient may decide which drink to have with the medicine. This freedom combined with the sophisticated yet simple drinking straw method distinctly contributes to a high compliance adherence. Additionally, the dose sipping syringe is designed to be re-used several times and hence is suitable for cleaning in the dishwasher.

Without any doubt, the awareness of the special requirements of paediatric drug delivery will significantly increase in the near future. RAUMEDIC already contributed to this emerging trend by the development of the above described devices. Of course, these devices are also beneficial for geriatric drug delivery since elderly patients often struggle similar issues than children (e.g., swallowing difficulties, non-compliance). Due to these reasons, RAUMEDIC is currently working on the development of further innovative drug delivery devices of the next generation.

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FDA: Contribution to developing pediatric formulations and transatlantic collaboration☆

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Pediatric drug products are pharmaceuticals intended for children ranging from birth till adolescence age. Since these products need to be administered to children across a broad age range. It is desirable that a platform technology would allow for easy titration to the desired dossier. Additionally a platform technology may entail a common formulation or novel drug delivery approach for a broad group of products with similar physicochemical properties, functional groups, and or pharmacokinetic properties. Such products must be easy to swallow and have acceptable organoleptic properties. The FDA-NIH intra agency collaboration was initiated with the aim of identifying drug products with pediatric needs, but lacking PhRMA interest for development, and to identify platform technologies based on the physico-chemical and pharmacokinetics properties of the drug substance. As an illustration of these platform technologies, a few drug substances will be selected for appropriate platform technology studies in the division of product quality laboratories.

Tablets are the most popular dosage forms among the general population as well as for the older, i.e., school age, children. For the children in the infants and toddler age groups liquid dosage forms such as drops, solution, suspension, etc. are preferred and may require an extemporaneous compounding from a tablet or capsule dosage form. In most cases, the solubility, stability and taste of

☆ The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination or policy.