Most of the VZV-infected children (t.i.d. treatment) rated the taste of the formulation as neutral, well liked, or very well liked, i.e. 69.8% at day 1 after the first dose in the clinic, 56.6% at day 1 after the first dose at home, and 69.8% at day 8 after the last dose at home.

For both HSV infected and VZV-infected patient populations combined, the aftertaste of the formulation was more pleasant than the taste immediately after swallowing.

Overall, caregivers indicated that nearly half of the children infected with either HSV or VZV considered famciclovir paediatric formulation to be well or very well accepted.

4. Conclusion

It is expected that the need for palatability studies in children will increase in the next decade as a consequence of the European Paediatric Regulation. In parallel taste and acceptability will need to be assessed in younger children. This will require more involvement of parents/caregivers/healthcare providers, wider use of already existing methods (e.g. medication acceptance scale) as well as the development of new reliable methods. It was demonstrated that formulation acceptability can be assessed as early as in the safety/tolerability study in children. However, in order to get taste information even earlier, when writing a PIP one should consider to use a similar methodology during safety/tolerability studies in adults.

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Regulatory aspects of devices

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Taking care of children and their needs can motivate innovation. For example in 1955, Susie, a 13-year old girl challenged her nebulizer and asked for a spray-like delivery system which was immediately invented by Thiel (1996). This was the birth of the p-MDI and it took from 1955 to 1956 for the development from invention to FDA approval, using a New Drug Application file which was 13 mm thick. Today, submission files (if printed out) count in meters and considerable manpower is consumed for creating and reviewing the paperwork. Lucky enough, children are not impressed by reports: they like their device – or not. For this reason industry and regulators should listen to the voice of the customer who is in this context the team made up of child and caregiver. In this respect, handling studies may be a feasible way to learn a good deal about the devices to come to the market.

At present 733 Paediatric Investigation Plans (PIPs) are listed on the EMA website (EMA, 2011). Table 1 gives an overview stating the frequency of PIPs in the therapeutic areas and the main pharmaceutical forms.

In Table 1, the most active areas are: pneumology–allergology (1), endocrinology (2), cardiovascular (3), oncology (4), infectious diseases (5), immunology (6), vaccines (7), and others. In the field of pharmaceutical forms, suspensions for injection (1) lead by far, followed by tablets (2), infusions (3), capsules (4), oral solutions (5), oromucosal drops/solutions (6), and then inhalation/nebulized solutions (7). Sublinguals (8) and other forms are less frequent.

From this table it is clear that high-tech devices e.g. inhalers and nebulizers form a minority in spite of the therapeutic area pneumology–allergology being in the first place. Looking into the details, the allergology is responsible for the high number of PIPs and in this indication suspensions for injections are very common. Within the combined indication pneumology–allergology inhalers take the 4th place after suspensions for injection (1), oromucosal drops/solutions (2), and oral solutions (3). Just because of their inherent technological challenges, inhalers will be used as example devices in this contribution.

The view on the regulatory workload gives a picture of the pediatric development landscape. Table 1 shows the present situation and dosage forms which are already coupled to their device. The future need for innovative devices is not necessarily correlated with the present number of PIPs and formulations included but a trend may be assumed. For this reason, syringes, tablet- and capsule-dispensers, infusion technology, dosing spoons, cups, and their alternatives, and finally inhalers are good candidates for innovation, assuming that the pharma market will not change dramatically.

So far we have considered devices in general which now must be assessed from a regulatory point of view. The first question to be answered is whether the device is a Medical Device according to the regulatory definitions. In Europe, the Directive 93/42/EEC (Council Directive 93/42/EEC 1993) and the Directive 90/385/EEC (Council Directive 90/385/EEC 1990) (both as amended (March 2010)) define 'Medical Devices', the latter relates to implantable ones. The Directives regulate the placing on the common European market and putting into service these devices. The Directives are intended to maintain or improve the level of health protection in the Member States. Future changes and national legislation of the Member States might add requirements. Compliance with the Directives is checked by a hierarchical chain from national governments, Competent Authorities, Notified Bodies as well as test

Table 1
Most frequent pharmaceutical forms as listed in Paediatric Investigation Plans (PIPs) published on the EMA website (EMA, 2011).

Therapeutic area	Suspension for injection	Tablets	Infusion	Capsules	Oral solution	Oromucosal drops/solution	Inhalation	Nebulizer solution	Number of PIPs
Gastroentology-hepatology	9	4	2	8	5				25
Immunology-rheumatology-transplantation	10	4	18	3	5			1	47
Neurology	8	11		4	6	2			28
Nutrition	1		2						3
Pain	2	15	1	4	5		1		25
Cardiovascular diseases	6	56	2	8	1		1	2	80
Other	3								10
Vaccines	26				1				31
Endocrinology,-gynacology-fertility-metabolism	25	58	4	10	2				102
Haematology-Hemostaseology	20	2	4	3	1				30
Oncology	16	16	22	12	2				67
Psychiatry	3	10		2	1				13
Uro-nephrology	3	5	1	4	1				13
Infectious diseases	2	26	18	3	7		1	1	48
Ophthalmology	6			1					20
Pneumology-allergology	67	8		2	20	27	11		143
Diagnostic	4				1				7
Anaesthesiology	3								4
Dermatology	8	1	1	1	2				24
Neonatology-paediatric intensive care	2		1						3
Oto-rhino-laryngology	1	4				3			10
Sum (multiple nominations of therapeutic areas possible)	225	220	76	65	60	32	14	4	

houses or laboratories. If a device complies with the definition of a Medical Device, it may fall into one of three classes, assessing the level of risk attributed to its use. Class I = low, Class IIa/IIb = medium, Class III = high risk. A Conformity Assessment will be performed depending on the Class and in the simplest case a self-certification by the manufacturer is sufficient in order to obtain the CE mark. The flow chart of several variants for the Conformity Assessment in Europe is given in Fig. 1.

Depending on the Class (I, IIa and IIb) the Technical File must be compiled and many Notified Bodies like to review it (Class IIa and IIb) because it provides information on the device and demonstrates that a product meets all Essential Requirements applicable. For more complex devices (e.g. Class III) the Design Dossier is required, being more detailed than the Technical File and reviewing the design and verification (e.g. clinical trial). The Design Dossier is examined by the Notified Body and a certificate is issued. While the pharmaceutical industry mainly relies on Pharmacopeia, Commission, ICH and CHMP guidance documents for the development of drugs and the corresponding legislation, Medical Devices are also subject to a compliance check with engineering standards which are created by experts not necessarily working in the field of drug development. For example, the European Standard EN ISO 20072:2010 (Aerosol drug delivery device design verification – Requirements and test methods) is in-between pharmaceutical and engineering science and therefore subject to heavy discussions.

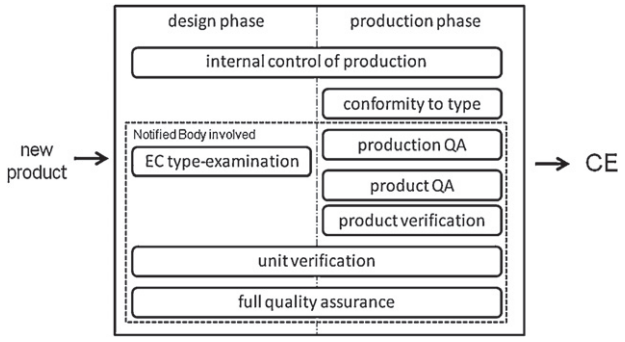

Fig. 1. Alternative routes of Conformity Assessments. One route is required for obtaining the CE-mark. Only for certain Class I devices the manufacturer may rely on internal control of production and self-certification. The dotted box indicates modules which involve a Notified Body.

In the US the classification of devices faces the same challenges as in Europe (U.S. FDA Medical Device Regulation: 21 C.F.R. Part 801). FDA has provided recently a Draft Guidance for Industry and FDA Staff recommending to contact the Office of Combination Products (OCP) to confirm the classification in case of doubt. A request for designation (RFD) will be answered within 60 days. If no answer is issued, the proposed classification by the manufacturer will be considered to be final. Medical Device Establishment Registration and Medical Device listings are required. Many Medical Devices require clearance by the FDA before they can be marketed in the US (U.S. FDA 510(k) overview). If a substantially equivalent device already exists, the FDA 510(k) Submission may clear the Medical Device for commercial distribution in the US (U.S. FDA 510(k) clearances). In case the device is referred to in other submissions to FDA, a New Medical Device Master File may be required.

Examples for the classification of devices now will focus on the EU regulations. The most frequently quoted example is the syringe, which is a Medical Device when sold as is, but being a prefilled syringe it falls into the group of Medicinal Products (not a device). Empty syringes (without needles) as well as cups and spoons intended for the administration of medicines are in Class I. Needles are in Class IIa.

Devices designed for children are covered by the existing regulations which require taking into account "ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety)" and "intended users (design for lay, professional, disabled or other users)". However, explicitly addressing children in the examples of intended users might be desirable. As the Technical File requires a pre-clinical and a clinical evaluation it is ensured that the device will be checked for its applicability to children as the intended users.

Most clinical studies focus on the summary effect produced by a certain device and the drug administered. From the device point of view it would be desirable to study the influence of the device on the final result and to include as many children as possible in such a study. This motivates handling studies which focus on device oper-

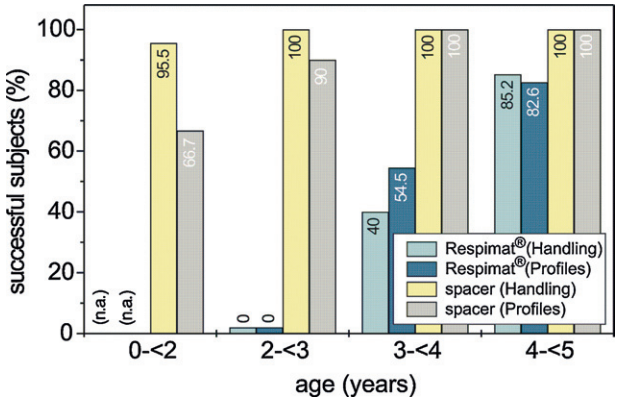

Fig. 2. Example of a handling study checking an inhaler with and without an accessory device. The percentage of successful subjects according to handling assessment or via air flow profile analysis is given, criterion = volume inhaled (acceptance level 0.15 L). Respimat® inhaler alone (with or w/o help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