Legin, A., Rudnitskaya, A., Clapham, D., Seleznev, B., Lord, K., Vlasov, Y., 2004. Electronic tongue for pharmaceutical analytics – quantification of tastes and masking effects. Anal. Bioanal. Chem. 380, 36–45.
Legin, A., Kirsanov, D., Rudnitskaya, A., Seleznev, B., Legin, E., Papieva, I., Clapham, D., Saunders, K., Richardson, M., 2011. Electronic tongue on a way towards the universal bitterness scale. In: AIP Conf. Proc., September 6, 2011 – 1362, pp. 93–95 (olfaction and electronic nose: proceedings of the 14th international symposium on olfaction and electronic nose).
Meltzer, E.O., Blaiss, M.S., Derebery, M.J., Mahr, T.A., Gordon, B.R., Sheth, K.K., Larry Simmons, A.L., Wingertzahn, M.A., Boyle, J.M., 2009. Burden of allergic rhinitis: results from paediatric allergies. J. Allergy Clin. Immunol. 124, S43–S70.
Milgrom, H., Bender, B., Ackerson, L., Bowry, P., Smity, B., Rand, C., 1996. Noncompliance and treatment failure in children with asthma. J. Allergy Clin. Immunol. 98, 1051–1057.
Shah, A., Ben-Shahar, Y., Moninger, T., Kline, J.N., Welsh, M.J., 2009. Motile cilia of human airway epithelia are chemosensory science. Science 325, 1131–1134.

http://dx.doi.org/10.1016/j.ijpharm.2012.05.056

Industry perspective on palatability testing in children—Two case studies

Gesine Winzenburg*, Sabine Desset-Brèthes

Technical Research & Development, Novartis Pharma AG, Basel CH 4056, Switzerland

E-mail address: Gesine.Winzenburg@novartis.com (G. Winzenburg).

1. Introduction

The development of age appropriate paediatric formulations is paramount to enable children adherence to treatment (Mennella and Beauchamp, 2008). It encompasses multi-dimensional considerations including the administration route, the formulation technology and the dosage strength. For oral treatments, palatability is crucial for children compliance to therapeutic regimens (Matsui et al., 1997). EMA Paediatric Investigation Plan (PIP) guidelines stress the particular relevance of taste masking and palatability testing in the development of oral treatment for children (EMA, 2007). The need for taste testing of new medicines was also recognized by the French Health Products Safety Agency, AFSSAPS, who is proposing paediatric taste acceptability studies for liquid antibiotic preparations (Cohen et al., 2009).

Therefore, taste masking and taste testing is becoming intrinsic to paediatric pharmaceutical development. The taste information can be derived from several methods like the electronic tongue, cell and animal based models and human panel testing (Anand et al., 2007). The taste testing in children is considered as the most reliable approach as the taste prediction by in vitro methods still lacks understanding while taste perception and preferences have been shown to be different from adults to children (Matsui et al., 1997).

However, carrying out taste tests in children is associated with a variety of practical, technical, ethical and regulatory challenges, including enrolment of children, lack of regulatory guideline, questionnaire design and reliability of paediatric responses (Cram et al., 2009).

General practical considerations related to palatability testing in children, e.g. questionnaire and response model design will be discussed. These will further be exemplified with 2 case studies.

1.1. Palatability studies

Palatability assessment typically comprises the taste assessment, e.g. the measure of the taste quality and intensity to encompass initial taste, aftertaste, flavour and texture. For this assessment, several types of questionnaire are used, including various types of response options. The mostly used response options types are (van Laerhoven et al., 2004):

- The verbal categorical response option is based on scoring of taste in a scale of e.g. 1 (very good) to 5 (very bad)
- The pictorial categorical response option (using a facial hedonic scale) allows expression of preferences using a pictorial scale
- Modified numeric response option is a combined visual analogue scale (VAS) and facial hedonic scale (Fig. 1)

Cognitive capabilities of the child have to be reflected in the design of the questionnaire and the choice of the response options model to ensure a reliable study assessment.

From 4 years onwards, children can generally well communicate their feelings and preferences and are therefore considered capable of participating in taste assessment trials (Sjovall et al., 1984). However, for children below 6 years, it is not recommended to use the facial hedonic scale alone as these young children may associate the facial pictures with other quality attributes (or their own mood) than the taste. In addition, they may not be able to express differences in taste perception and rank formulations. Therefore for children below 6 years it is recommended to use the child's own spontaneous verbal judgment following a control question when comparing different formulations (Anand et al., 2008). In order to improve the reliability of the study outcome, parents, caregivers and/or health providers should be involved in the study and asked to report about any discomfort or other observations in relation to acceptance of the study medication (e.g. spitting out of the medicine).

For children younger than 4 years of age neither the spontaneous verbal judgment nor the facial hedonic scale can be used as they have limited ability to communicate, understand the questionnaire and follow the study instructions. Hence, the questionnaire is designed and limited to collect the observations and their interpretation from parents, caregivers and/or health providers only. Therefore alternative response models can be used like the facial coding system for pain quantification or the use of behavioural elements of the medication acceptance scale, e.g. cry, facial expression or body movement (Kraus et al., 2001).

Two case studies (at a late stage and an early stage of pharmaceutical development) of palatability assessment in children are discussed in the following paragraphs. More detailed information regarding the methods and results can be accessed in the original papers Abdulla et al. (2010) and Saez-Llorens et al. (2009), writ-

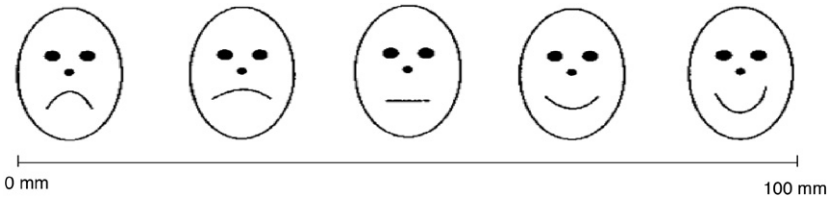

Fig. 1. Modified visual analog scale including a 5-point hedonic scale often used to assess the palatability of paediatric formulation.

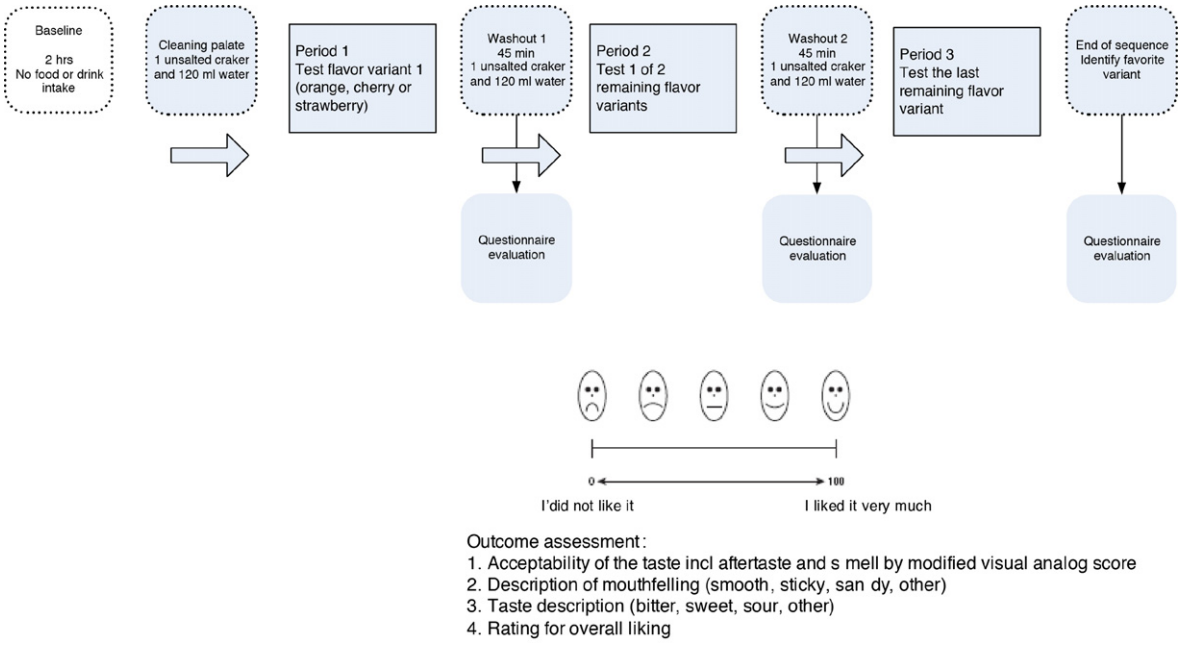

Fig. 2. Study design of Coartem® palatability study in children.

ten by the group of persons who developed the methodology and performed the testing and its evaluation.

2. Palatability assessment of an oral anti-malarial product for children

2.1. Background

When treating infants and young children against malaria, the Coartem® tablets, containing 20 mg of artemether and 120 mg of lumefantrine, usually have to be crushed prior to administration to overcome hurdles associated with swallowing. The crushed tablets, similarly to other anti-malarials, have a bitter taste that may cause children to spit out the medication with the risk of misdosing (Abdulla and Sagara, 2009). Therefore a dispersible tablet was developed to provide a medication to children that is easy to swallow. The bitter taste of the active compounds was masked with the help of sweeteners and flavours. In order to ensure children adherence to the treatment a palatability study was conducted to compare 3 most promising formulations, containing cherry, strawberry and orange flavours respectively.

2.2. Methods

The palatability study was conducted as a swill and spit taste study in 48 healthy children (24 girls and 24 boys) aged 7–10 years (mean age 8.6 years and standard deviation ± 0.7 years) originating from Tanzania, East Africa. The study protocol was reviewed and approved by the Independent Ethics Committee of the Ifakara Health Institute (Dares Salaam, Tanzania) and written informed consent was obtained from the parents or legal guardians and also assent was obtained from the children. The subjects who were able to hold 2 ml of apple juice in their mouth for 10 s without swallowing and have completed a questionnaire were enrolled in the study. When enrolled, the subjects received 2 ml of an oral suspension containing 120 mg of artemether and 120 mg of lumefantrine (strawberry-, orange- or cherry-flavoured) in a randomized, single-blind, crossover design. The amount given represented half of the treatment dose for children of this age. The study medication was administered into the mouth cavity using a 10 ml plastic syringe. Following the administration, the subject swilled the drug suspension in the mouth cavity and then held it in the mouth for approximately 10 s before spitting it out. All the formulations had a yellow appearance to prevent any bias. No food or beverage was allowed for 2 h before the study commenced. The three administrations were performed within one day, separated by 45 min intervals. Immediately after each test dose, the child was asked to separately rate the flavour, smell, sweetness and overall liking of the medicine using a modified 100 mm visual analogue scale (VAS) that incorporated a facial hedonic scale (Angelilli et al., 2000; Freedman et al., 2010). The aftertaste was assessed by rating of overall liking 2–5 min after the study drug had been spat out. In addition, approx. 15 minutes after the last administration had been rated the children were asked about their preferred formulations (a ranking from 1 to 3 was performed) (Fig. 2).

2.3. Results

All flavours were highly rated with mean VAS scores ranging between 70 and 87 mm with no significant gender difference. There was no significant difference in pooled VAS scores between the three flavours for any rating. The analysis of the formulations ranking on the overall preference also indicated no significant difference ($P = 0.146$). Numerically, cherry had the highest score in overall liking (immediately after administration) and in the rating for flavour (Fig. 3) and was therefore selected for further development.

In the first case study, the taste was assessed in a standalone palatability study in children for the selection of the formulation intended for the market. In the second case study, the taste assessment was performed in the target paediatric population and embedded in the early phase clinical study for safety and tolerability testing.

3. Palatability assessment of an antiviral product in children

3.1. Background

Intravenous and high-dose oral acyclovir is the gold standard for many children requiring treatment and/or prevention of her-

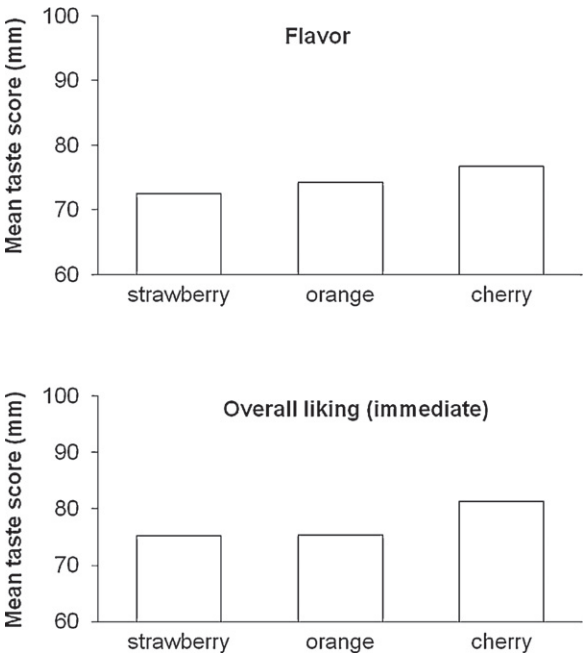

Fig. 3. Mean VAS palatability scores (24 girls, 24 boys). [I did not like it] = VAS score of 0 mm; [I liked it very much] = VAS score of 100 mm (data not shown for aftertaste, smell and sweetness).

pes simplex virus (HSV) and varicella-zoster virus (VZV) infections (Saez-Llorens et al., 2009). However, intravenous acyclovir requires hospitalization, and acyclovir is not ideal for oral administration to children mainly due to limited bioavailability that requires frequent dosing. Only few alternative therapies for treating HSV infections are available for children. Therefore, famciclovir (Famvir®) was tested in single and multiple dose safety/tolerability and acceptability studies in children 1–12 years old (Fig. 4).

Famciclovir is formulated for adults as film coated tablet. For children, an exploratory formulation was developed, i.e. Famciclovir "sprinkle granules", filled in hard gelatin capsules. The capsules are meant to be opened and their content to be mixed with OraSweet® syrup vehicle shortly before intake.

3.2. Methods

The acceptability of the famciclovir paediatric formulation was assessed after the single dose and the first, second, and last doses in a multiple dose study. The assessment was done immediately after swallowing and 2–5 min later. A modified five point facial hedonic scale was used for the rating. Children older than 5 years completed the questionnaire themselves, while parents/legal guardians completed the questionnaire for younger children. In addition to the hedonic scale, caregivers provided a study medication acceptability response (i.e. how well the child accepted the medication) for all children.

3.3. Results

3.3.1. Single-dose study

Most children liked the taste of the famciclovir formulation administered however the aftertaste was found to be more pleasant than the taste immediately after swallowing. Overall, the caregivers considered famciclovir paediatric formulation to be well or very well accepted in 67% of the children. However, the caregivers reported that 15.7% of participants disliked the taste of the medication.

3.3.2. Multiple dose study

The majority of HSV-infected patients (b.i.d. treatment) rated the taste of the famciclovir formulation as neutral (i.e. neither good nor bad): 53.2% at day 1 after the first dose in the clinic, 61.7% at day 1 after the first dose at home, and 63.8% at day 8 after the last dose at home.

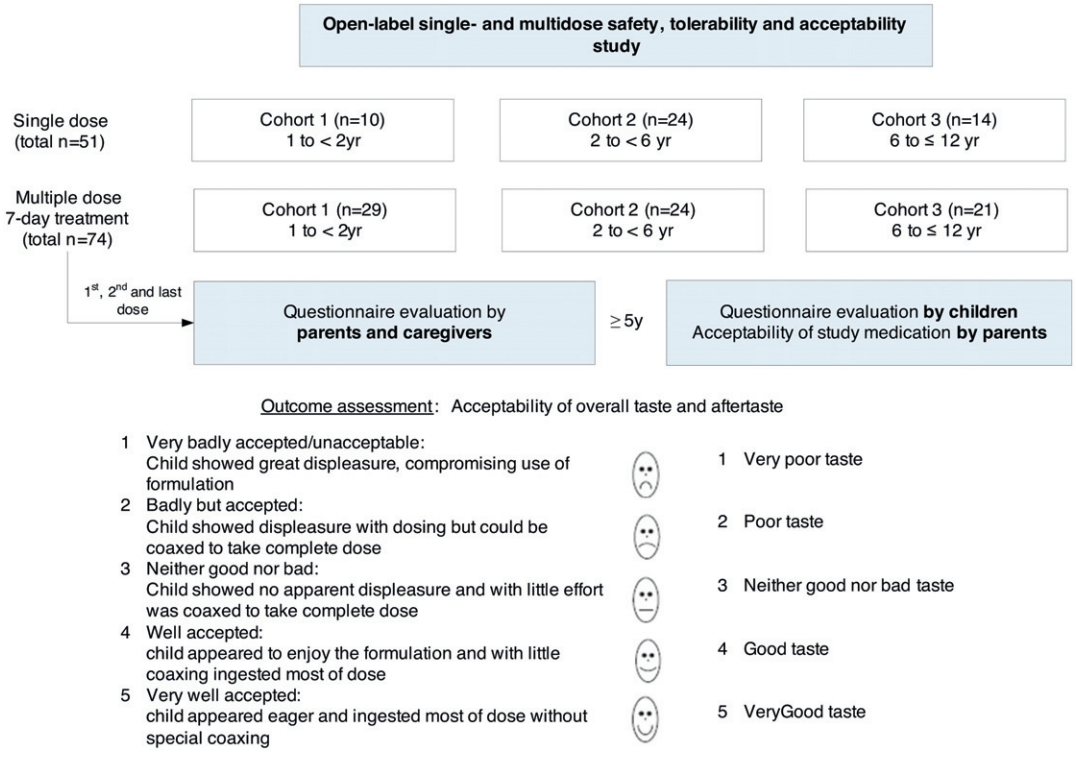

Fig. 4. Study design of Famvir® pharmacokinetic study including safety, tolerability and acceptability in children.

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.

References

Abdulla, S.B., Amuri, A., Kabanywanyi, M., Ubben, D., Reynolds, C., Pascoe, S., Fitoussi, S., Yeh, C.-M., Nuorttio, M., Séchaud, R., Kaiser, G., Lefèvre, G., 2010. Early clinical development of artemeter-lumefantrine dispersible tablet: palatability of three flavours and bioavailability in healthy subjects. Malaria J. 9, 253.

Abdulla, S., Sagara Isaka, 2009. Dispersible formulation of artemether/lumefantrine: specifically. developed for infants and young children. Malaria J. 8 (suppl 1), S7.

Anand, V., Kataria, M., Kukkar, V., saharan, V., Choudhury, P.K., 2007. The latest trends in the taste assessment of pharmaceuticals. Drug Discov. Today 12, 257–265.

Anand, V., Kharb, V., Kataria, M., Kukkar, V., Choudhury, P.K., 2008. Taste assessment trials for sensory analysis of oral pharmaceutical products. Pak. J. Pharmaceut. Sci. 21, 438–450.

Angelilli, M.L., Toscani, M., Matsui, D.M., Rieder, M.J., 2000. Palatability of oral antibiotics among children in an urban primary care center. Arch. Pediatr. Adolesc. Med. 154, 267–270.

Cohen, R., de La Rocque, F., Lecuyer, A., Wollner, C., Bodin, M.J., Wollner, A., 2009. Study of the acceptability of antibiotic syrups, suspensions, and oral solutions prescribed to pediatric outpatients. Eur. J. Pediatr. 168, 851–857.

Cram, A., Breitkreutz, J., Desset-Brethes, S., Nunn, T., Tuleu, C., 2009. Challenges of developing palatable oral paediatric formulations. Int. J. Pharmaceut. 365, 1–3.

EMA. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December (2006) on Medicinal Products for Paediatric Use, 2007.

Freedman, S.B., Cho, D., Boutis, K., Stephens, D., Schuh, S., 2010. Assessing the palatability of oral rehydration solutions in school-aged children a randomized crossover trial. Arch. Pediatr. Adolesc. Med. 164, 696–702.

Kraus, D.M., Stohlmeyer, L.A., Hannon, P.R., Freels, S.A., 2001. Effectiveness and infant acceptance of the Rx medibottle versus the oral syringe. Pharmacotherapy 21, 416–423.

Matsui, D., Lim, R., Tschen, T., Rieder, M.J., 1997. Assessment of the palatability of beta-lactamase-resistant antibiotics in children. Arch. Pediatr. Adolesc. Med. 151, 599–602.

Mennella, J.A., Beauchamp, G.K., 2008. Optimizing oral medications for children. Clin. Therapeut. 30, 2120–2132.

Saez-Llorens, X., Yogev, R., Arguedas, A., Rodriguez, A., Spigarelli, M.G., Castrejon, T.D.L., Bomgaars, L., Roberts, M., Abrams, B., Zhou, W., Looby, M., Kaiser, G., Hamed, K., 2009. Pharmacokinetics and safety of famciclovir in children with herpes simplex or varicella-zoster virus infection. Antimicrob. Agents Chemother. 53, 1912–1920.

Sjovall, J., Fogh, A., Huitfeldt, B., Karlsson, G., Nylen, O., 1984. Methods for evaluating the taste of pediatric formulations in children—a comparison between the facial hedonic method and the patients own spontaneous verbal judgment. Eur. J. Pediatr. 141, 243–247.

van Laerhoven, H., van der Zaag-Loonen, H., Derkx, H.H.F., 2004. A comparison of Likert scale and visual analogue scales as response options in children's questionnaires. Acta Paediatr. 93, 830–835.

http://dx.doi.org/10.1016/j.ijpharm.2012.05.057

Regulatory aspects of devices

Herbert Wachtel

Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Str. 173 55216 Ingelheim, Germany

E-mail address: herbert.wachtel@boehringer-ingelheim.com.

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