OPINION

The Emperor's New Clothes II—time for regulators to wake up and take responsibility for unnecessary asthma morbidity: time for the second aerosol 'transition'

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ABSTRACT

The rate of technological improvement continues to accelerate. Regulators in every field dealing with consumer products continue to set ever higher standards to protect consumers from adverse events and use 'recalls' to remove products that prove to be harmful from the market. In the field of medical products in general the issues of 'human factors' and 'usability' are now, quite rightly, a major issue at least among regulators in the USA. The elephant in the inhaled therapy room is of course the continued use of obsolete, portable inhalers which few patients can use effectively for the treatment of asthma. Countless studies have demonstrated that the inability of patients to use these devices effectively is a major factor in perpetuating unnecessarily high levels of morbidity. They fail to meet basic usability standards and do not incorporate the facility to provide feedback to patient and clinician. More than 20 years ago regulators deemed that pressurised metered dose inhalers containing chlorofluorocarbons should be removed from the market on environmental grounds even though their use accounted for less than 0.5% of chlorofluorocarbon use. Surely asthmatic patients require the same level of protection. Unfortunately regulators appear determined to fossilise the field in a 1950's time warp by ensuring that the failings of obsolete technology are perpetuated in any 'generic' device. The time has come for regulators to meet their obligations to *'protect the public health by assuring the safety, effectiveness, and security of drugs, vaccines and other biological products, medical devices….'* and mandate the phasing out of these antiquated devices within the next decade in order to reduce the unacceptably high burden of preventable morbidity and death associated with their use.

THE FIRST AEROSOL 'TRANSITION'

More than half a century has passed since the pressurised metered dose inhaler (pMDI) was invented—a brilliant solution to the then current problem of fragile, inconvenient single dose glass handheld nebulisers delivering adrenalin which were the only portable delivery systems at that time.[1] It was known within a very short time that reproducibility of lung dose when using pMDIs was poor and that many patients lacked the competence to use the devices effectively even after training. For a drug such as salbutamol, with a wide therapeutic index, this is of limited consequence as a high dose can compensate for inefficient drug delivery and the close temporal relationship between taking the medication and response allows patients to repeat doses if the response is suboptimal due to poor technique. Despite this knowledge the first inhaled corticosteroid (ICS), beclometasone, was marketed in a pMDI in the early 1970s with little consideration given to the development of a delivery system that patients *could* and *would* use regularly and effectively.

In the late 1980s the Montreal agreement led to the 'chlorofluorocarbon-transition' which provided an opportunity to revisit the usability of delivery devices for ICS. However the pharmaceutical companies chose to perpetuate a situation known to be associated with a substantial unnecessary morbidity in the belief that this would be the simplest and cheapest option. The 'transition' proved to be much more difficult and expensive than expected with the estimated cost being in excess of $4 billion. While many clinicians were persuaded by the pharmaceutical companies that the 'transition' was a good thing, there were some dissenting voices who argued that the key issues of adherence and device compliance (usability) were not being addressed.[2] It should also be noted that patient activated dry powder devices have essentially remained unchanged for a similar period of time and have similar problems.

WHAT ARE THE KEY ISSUES?

As we proceed through the second decade of the 21st century the list of publications highlighting the difficulties that patients experience grows ever longer. Asthmatic patients continue to experience substantial levels of unnecessary morbidity, and indeed mortality, directly attributable to low levels of true compliance (adherence x device compliance). Because current devices are not intuitive to use, patients may derive little or no benefit from their ICS inhaler even if they use it regularly because they lack the competence to use it effectively or contrive to use it ineffectually.

Of equal importance, current devices conspicuously fail to deal with the issue of adherence. The inhaled route is used for ICS as they have a good risk/benefit ratio if used regularly, effectively and at approved doses. However it is clear that the onset of action is relatively slow while the offset, if doses are omitted, is very rapid. A review of the literature

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suggests that for those with significant symptoms and/or exacerbations patients should be taking 80% or more of the prescribed doses, a level that appears to be achieved by a minority of patients. There is a growing body of evidence that providing feedback to patients either directly via the device or via the healthcare professional, thus facilitating an open and honest discussion between the healthcare provider and the patient, can significantly improve adherence with benefits to the patient and healthcare providers.

The fossilisation of inhaled therapy in the 1950s is in stark contrast with other areas. In the 1950s the concept of playing music on a tiny portable device such as a mobile phone that also allowed you to search the internet, have a built in camera and numerous other functions would have been seen as fanciful science fiction. It is necessary to understand that the situation relating to the perpetuation of a 60-year-old technology is due to regulatory and commercial considerations and not due to lack of technological progress. The expertise to develop devices that meet the standards one would expect in the second decade of the 21st century is available—indeed over the past two decades there has been a vast investment in inhaler technology that has focused as much on patient factors as on the mechanism of aerosol generation. Unfortunately the regulatory and commercial environment has precluded developing these devices for the benefit of asthmatics leaving the device companies to search for new chemical entities to partner their device. The Exubera device for insulin is just one of the many developed over the past two decades. Its approval and use in clinical practice demonstrated that reproducible, and perhaps more importantly, reliable doses can be delivered when a device is designed with the patient in mind. In addition to developing intuitive devices that reliably deliver drug to the lungs the incorporation of data loggers is likely to contribute to substantial improvements in care. The dramatic strides in battery and electronic technologies during the past decade have taken this from a desirable but impractical option to one that could be very cost effective.

WHY HAS THERE BEEN SO LITTLE PROGRESS IN RECENT DECADES?

Responsibility must be distributed between clinicians, drug companies and regulators with regulators increasingly being seen as the greatest impediment to progress.

Clinicians are responsible in that despite the evidence that patients find current devices difficult to use they have, as a whole, failed to demand change and advocate for their patients. This is probably in large part due to a lack of understanding of this key component of respiratory care. Aerosol therapy can appear to be complicated and 'best left to the experts' when in fact the basics are simple but rarely taught.

Pharmaceutical companies clearly have a role. As their title suggests they are primarily interested in drugs and in general they appear to be driven by a belief that the answer to loss of patents is to find a new blockbuster drug. They are not generally interested in the delivery system unless it is critical for an application. The failure of inhaled insulin will have confirmed to many that new chemical entities or biologics are the areas in which to invest.

Regulators have conspicuously failed to deal with the issues of 'usability' and, more recently, the need to incorporate the ability to provide feedback. To these sins of omissions they have compounded the problem by placing unnecessary hurdles in the path of generic companies. At times it appears baffling that regulators can waste so much time, money and energy in trying to perpetuate every small failing of 60-year-old devices. While they would argue that this is to 'protect patients' an alternative view would suggest that all this activity is largely a form of displacement activity permitting regulators the opportunity to ignore the elephant in the room—the fact that a huge number of patients are harmed because they cannot or do not use inhalers regularly and effectively.

It should be noted that some of the actions of regulators are justified since concerns regarding the potential of 'more efficient' devices to cause harm are not without foundation as highlighted by recent concerns regarding the safety of tiotropium delivered via the Respimat device as compared with the more difficult to use and 'less efficient' Handihaler.[3] However this is not an issue of usability but of dose delivered and, as in all cases, is drug specific. Trying to match the performance of new generic devices for asthmatic patients with every last flaw of the 'reference' product is absurd since the reality is that the *inter* and *intra* subject variability in lung dose when patients use current (obsolete) inhalers is so large that it is impossible to predict the effect of changing a patient from one inhaler to another and hence the only effective guide to the correct dose of an ICS is to use the lowest effective dose as noted in the current SIGN/BTS guidelines.

The issue of harm caused by approved medical devices has become increasingly topical and the large number of recalled products, including the recent breast implant scandal, has highlighted failings in the approval process and postmarketing surveillance. The US Food and Drug Administration's current focus on 'usability' and 'human factors' demonstrates[4 5] that they are aware of the issues and are incorporating these requirements into the development of future devices but do not appear to have grasped the need to address the issue in respect of current inhaler devices. Extraordinarily currently European regulators do not have any guidance in these respects. One might suggest that their failure to act leaves them open to a class action from those who have experienced morbidity as a result of being prescribed devices that are not fit for purpose. While serious harm can result from overdosing, much more harm is currently caused by failure to obtain a therapeutic effect. The former is most commonly due to clinicians who misdiagnose or mismanage asthma, the latter because patients are prescribed devices they cannot use effectively.

SUMMARY

It appears to be scandalous that well into the 21st century patients are confronted with devices that are not intuitive to use and which do not deal directly with the issue of adherence when the technologies to solve these problems are readily available. Desirable attributes would include being intuitive to use; achieving reliable drug delivery to the lungs; preventing misuse due to poor competence or contrivance and actively promoting adherence through feedback. The current challenge is to marry very effective drugs in the form of ICS with effective delivery systems. Sadly neither the twain shall meet until regulators act in accordance with their responsibility for protecting patients. A wholesale recall of inhaled products is clearly not possible but alternative strategies as seen with the first transition are available including the provision of deadlines for transition based on a date or the appearance of the first marketed product. The only possible argument against regulators taking a radical approach to this problem is that there will be a cure or incredibly effective new therapy that makes ICS therapy for asthma redundant. At present there is no realistic prospect of either in the next decade and hence clinicians should be advocating for their patients and demanding the regulators meet their obligations to '*protect the public health by assuring the safety, effectiveness,*

and security of drugs, vaccines and other biological products and medical devices….'.

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