The history of inhaler development in modern times can be traced to the metering valve and propellants (pressurized metered-dose inhalers [pMDIs]) used in the delivery of therapies for the treatment of asthma in the 1950s (3). This was followed closely by the somewhat-primitive dry-powder inhalers (DPIs) in the 1970s (Intal-Cromolyn-A Monograph, Fisons Corporation, Bedford, MA, 1973). Throughout this period nebulizers were used to deliver drugs in an aqueous solution. However, the solution was dispensed independently of the nebulizer, and the two substances were combined in the home or the hospital. Recently, aqueous-solution metering systems have been developed that are handheld and similar in application to pMDIs and DPIs (4,5).

Since our review in 1997 (1), research and development activity in this field has broadened. This may be explained in part by the demise of the Kyoto Treaty on Global Warming (6), which has refocused activities in the area of alternative propellant formulation. More important, research into alternative approaches to powder and solution formulation and stability has increased. This review is intended to reflect the interest and growth that have occurred in the field of pharmaceutical inhalation aerosol technology in the past four years.

pMDI devices
PM DIs have been used for more than 40 years and are well accepted by most patients as a means of administering medication. They are the most widely used inhalation delivery device, with an estimated 800 million units produced in the year 2000 (7). Traditional pMDI systems comprise an aerosol container, a metering valve, a drug substance in suspension or solution, excipients, and a liquefied propellant that provides the energy for aerosolization. Dose administration typically involves depressing the valve via an actuator that also functions as a mouthpiece. Despite the popularity of pMDIs, these systems have some disadvantages (see Table I). Many of the advances in pMDI device and formulation technology during the past 10 years have sought to address these deficiencies. A specific event that initiated much of the progress seen in recent years was the 1987 signing of the Montreal Protocol on Substances that Deplete the Ozone Layer.

Worldwide concern over the possible deleterious effects of chlorofluorocarbons (CFCs) on the stratospheric ozone led to the signing of the Montreal Protocol, which committed the signatory nations to cease production of CFCs by 1996. Although specific exemptions, which were defined as essential, were granted for uses of CFCs, the pharmaceutical industry was forced to find alternative propellants for pMDIs. The existing pMDI propellants — CFC 11, 12, and 14 — had no immediate replacements. However, because several hydrofluoroalkanes (HFAs) shared similar desirable characteristics (nonflammable, chemically stable, similar vapor pressures, and non-ozone depleting), they were investigated as possible substitutes for CFCs. The existing pMDI propellants — CFC 11, 12, and 14 — had no immediate replacements. However, because several hydrofluoroalkanes (HFAs) shared similar desirable characteristics (nonflammable, chemically stable, similar vapor pressures, and non-ozone depleting), they were investigated as possible substitutes for CFCs. After extensive testing, the propellant tetrafluoroethane (HFA 134a) was demonstrated to have toxicology and safety profiles at least as safe as CFC propellants and since then has been incorporated into pMDIs approved by regulatory agencies (7–9).

Despite the similarities with the CFCs, many additional difficulties in substitut-
Formulation-related pMDI advances

Propellant patents. The patent literature from the past decade reveals significant research into alternative propellant systems for pMDIs (patents may be searched online at www.uspto.gov). Many of the patents refer to HFAs and, in particular, to HFA 134a and/or HFA 227 combinations with cosolvents (e.g., US Pat. No. 6054488, WO 99/965460). It must be noted that many patents have been or are subject to legal opposition, and it is still unclear which patents will be upheld (10). Alternative propellants such as compressed gases (US Pat. No. 6,032,836), dimethylether, and propane (12) also have been investigated.

Excipients. Many of the surfactants used in stabilizing suspension formulations in CFC propellants have much-reduced solubility in HFA systems (13). The lowered surfactant concentration in HFA formulations adversely affects suspension stability and dose reproducibility because of rapid particle agglomeration and settling. Recent examples of efforts to overcome the complexities of suspension stability in HFA propellants include:
- encapsulation of drug particles (Canadian Pat. App. No. 2,136,704)
- use of perforated microparticles (WO 99/16422).
- use of other stabilizing excipients (US Pat. No. 6,136,294).

Device-related pMDI advances

Containers, valves, and seals. Compatibility of propellants, excipients, and solvents with the components of the valve and container greatly influences performance of pMDIs. Conventional materials used with CFCs have been found to sometimes cause suboptimal operation of the device because of elastomer swelling, extraction, poor lubrication, and adsorption of the formulation to container walls (14). Examples of recent patents dealing with such issues include US Pat. No. 6,006,745 that describes polymer materials for metered valves that are compatible with HFAs and US Pat. No. 6,143,777 that describes coating the inside of aerosol containers with fluorocarbon and nonfluorocarbon polymers.

Actuation mechanism. As outlined in Table I, a major concern of pMDI delivery is the requirement for patients to synchronize their breathing inspiration with the actuation of the aerosol device. Poor patient technique with pMDI use is reported to occur in about 38% of users (15). Thus, certain strategies have been used to assist in the coordination of inhaler actuation with patient breathing patterns. A well-known example is Smartmist (Aradigm, Hayward, CA), which analyzes inspiratory flow rates and automatically actuates the pMDI on the basis of this information. A similar concept of a breath-activated pMDI is described in WO99/65551, and US Pat. No. 6,095,141.

Spacers, plume modifiers. In addition to differences in solubility characteristics, HFA and CFC propellants have different vapor pressures (11,16). The higher vapor pressure of HFA 134a can result in increased plume velocities, leading to greater impact of the aerosol in the oropharynx (17). This inertial deposition causes poor delivery to the lung (18). Several different approaches to reducing oropharyngeal deposition include:
- added spacer devices or integrated spacer mouthpieces, e.g., Azmacort pMDI (Rhône-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, PA), Aerohaler (Bespak, UK), Spacehaler (Evans Medical, UK)
- decreasing plume velocity using airflow modifications within the device housing (e.g., US Pat. No. 6,062,214 describes a mouthpiece that creates a vortex airflow using a restrictive duct, and US Pat. No.

Table I: Pros and cons of pMDIs (97).

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portability and durability</td>
<td>Time-dependent dose variation (shaking, priming, dose tailing)</td>
</tr>
<tr>
<td>Active delivery (requires little inspiratory effort)</td>
<td>Cold sensation because of propellant evaporation</td>
</tr>
<tr>
<td>Long shelf life</td>
<td>Oropharyngeal deposition because of high aerosol velocities</td>
</tr>
<tr>
<td>Microbial robustness</td>
<td>Coordination of breathing required during actuation</td>
</tr>
<tr>
<td>Low cost of production</td>
<td>Variable deposition depending on inhalation maneuver</td>
</tr>
<tr>
<td>Environmental concerns</td>
<td>Environmental concerns</td>
</tr>
</tbody>
</table>

Figure 1: Areas of advancement in pMDI technology.
estimated that by 2005, HFAs from pMDIs without emission reduction limits, it is estimated that by 2005, HFAs from pMDIs will contribute less than 0.1% of the total worldwide greenhouse emissions (20). Thus it is likely, given the Montreal Protocol experience, that HFA propellants will be around for use in pMDIs for at least the next two decades.

**Aqueous delivery systems**

Nebulizers are drug delivery systems that can be used to generate solutions or suspensions for inhalation. Nebulizers have some advantages over pMDIs and DPIs. These devices typically are capable of producing small droplets from a solution or suspension that are suitable for deep lung delivery (1). Patient coordination of aerosol delivery is not as critical for achieving a therapeutic effect as it is for pMDIs or DPIs. In addition, aqueous solutions are often easily formulated for use in nebulizers and other aqueous delivery systems (13). Two types of nebulizers currently are marketed: jet and ultrasonic. Jet nebulizers use the Venturi Effect to draw solution through a capillary tube and disperse droplets in air at high velocity. Ultrasonic nebulizers use an oscillating, ultrasonic vibration that is conveyed by means of a piezoelectric transducer to a solution that creates droplets suitable for inhalation (13). Nebulizers are not portable and require an external source of energy. Recently, aqueous delivery systems have been developed to overcome these problems.

A portable, battery-powered aerosol generator has been developed (AeroGen, Sunnyvale, CA) to deliver aerosols from drugs in solutions or suspensions. The inhaler consists of a curved aperture plate placed in the actuator mouthpiece that vibrates when electrical energy is applied. The vibrations cause the solution or suspension to come in contact with the concave side of the plate and pass through the orifices, resulting in an aerosol (4). This device allows the aerosol particle size to be adjusted by changing the size of the orifices. Another advantage is the flexibility of dosing; one can select single or multiple doses from a container. The device is breath-actuated, allowing for reproducible dosing. In addition, the system has been shown to be suitable for the delivery of liposomes (23). The device can be used to store freeze-dried compounds, which can be dissolved in a solution (also stored in the device) immediately before being aerosolized. This is particularly useful in the case of proteins and peptides, which are more stable in the solid state (1).

Another breath-activated, aqueous delivery system, the AERx (Aradigm), has been developed (4) and was described in a previous review (1). This system has been shown to be useful in the delivery of peptide drugs (25), narcotics (26), and insulin (27).

A portable, piezoelectric aqueous delivery system has been developed for the delivery of drugs in solution (see Figure 2) (28). The device incorporates a breath-activated piezoelectric dispenser head, and a sensor and controller are used to control the dose delivered depending on the inhalation flow rate generated by the patient. The inhaler can be used for the delivery of analgesics, peptides, and proteins.

A portable, breath-activated delivery system, the Halolite (Medic-Aid, UK) has been developed with a deflector to switch on the aerosolization of a solution during inspiration and switch it off during exhalation (see Figure 3). It also monitors the inspiratory flow for three cycles and then generates the aerosol at the appropriate point on the inspiratory cycle. The device is capable of producing a precise dose and prevents waste of the drug during exhalation (29).

A device that uses an electric field to form an aerosol of fine droplets from a liquid has been developed (see Figure 4) (Battelle Pulmonary Therapeutics, Columbus, OH) (30). The aerosol formed from this system is almost monodisperse. The total delivered dose, dose reproducibility, and particle-size distributions generated...
few years, surprisingly few mechanisms are used to disperse powdered pharmaceuticals. Modifying the powder formulation is another research approach used to improve dispersion and is discussed in the next section of this article.

DPIs can be divided into two classes: passive and active devices. Passive devices rely solely upon the patient's inhalatory flow through the DPI to provide the energy needed for dispersion. This method has the advantage of drug release automatically coordinating with the patient's inhalation (1). The disadvantage is that dispersion typically is highly dependent on the patient's ability to inhale at an optimum flow rate. Depending on the inhaler design, this requirement may be difficult for some patients if the device's resistance to airflow is high (32). Active devices have been under development for the past 10 years, but no active device has been approved yet. Similar to pMDIs, active devices use an external energy source for powder dispersion. This has the advantage of potentially reducing the dependence of uniform dosing on the patient's capabilities. However, without a feedback mechanism for the energy source, it is still possible that different patients will receive different doses. In addition, the complexity of these devices likely has contributed to their inability to achieve regulatory approval, which also could increase their cost.

Passive devices have progressed in their complexity and performance since the introduction of Allen & Hanbury's Rotahaler and Fison's Spinhaler in the 1970s (33). The bulk of recent development in DPI technology has occurred at industrial organizations. Many of the technologies developed are not yet named. Therefore, in many cases, the US patent number is cited rather than a trademark name. Little published data other than the patent descriptions are available for most of the DPI technology discussed. Figure 5 divides mechanisms of dispersion into active and passive means, and the complexity of the mechanism is shown. The figure is not intended to represent the overall complexity of the device but only the dispersion mechanism. For example, many current designs include add-ons such as dose-counting means or dispersion indicators. The complexity of these features is not discussed.

Passive dispersion relies on the airflow generated by the user to aerosolize the powdered drug. All passive devices disperse the drug by passing the airflow through the powder bed. Early devices had very low dispersion of respirable-sized particles, often around 10% (34–36). In general, this poor performance can be attributed to the incomplete deaggregation of smaller drug particles from larger carrier particles used as an aid to powder flow during dispersion. More modern devices use means of generating significant turbulence to aid in the deaggregation process. Turbulence can be provided by tortuous flow paths for the particle-laden airflow as in the AstraZeneca Turbuhaler, the Schering-Plough Twistihaler, and US patent 5,469,843; by changing the dimensions of the airflow path (US Pat. 5,437,271); or by using impactor plates that also reduce the emission of large particles (US Pat. No. 5,724,959). A device developed by Innovative Devices (US Pat. Nos. 6,209,538 and 5,988,163) addresses the desirability of dispersing powder at optimal flow rates via channels in which operation is flow dependent. Initially, flow is diverted around the drug and is allowed to pass through the drug only when the optimal flow rate has been obtained. This device bridges the gap between passive and active devices by adding active features to a passive device.

Active devices use mechanisms such as springs or batteries to store energy that can be released to facilitate powder dispersion. The best-known active devices are the delivery systems from Inhale (San Carlos, CA) and the Spiros inhalers from Dura (San Diego, CA). The Inhaler device uses compressed air generated by the user through a spring-loaded pump mecha-
nism to disperse the powdered drug. A few other patents identified in Figure 5 use compressed air (US Pat. Nos. 5,875,776 and 6,003,512) or a vacuum (US Pat. No. 6,138,673) to provide energy for dispersion. The Spiros DPI uses a battery-driven impeller to disperse drug powder. The impeller operates only when the patient inhales through the DPI to ensure that dosing does not occur when not in use (37). Only one other mechanism of dispersion has been patented. This mechanism uses a hammer or other means of impact to dislodge drug from a powder bed typically contained on a blister strip (US Pat. Nos. 5,469,843, 5,482,032, and 6,142,146). Few published data are available for the active devices because most of their development has occurred in a proprietary atmosphere. Some of the patented technology, both for active and passive devices, is only conceptual.

**Powder formulations**

For lung deposition, drug particles generally are required to be smaller than 5-µm aerodynamic diameter. They may be prepared using either size-reduction methods such as milling or particle-construction methods such as condensation, evaporation, or precipitation (31). Historically, respirable particles are produced by jet-milling, where there is little control over the particle size, shape, or morphology (38). The resulting fractured particles are highly electrostatic and cohesive. Alternative methods of particle generation include spray-drying, solvent evaporation or extraction, and supercritical fluid condensation (39).

Particles smaller than 10 µm generally exhibit poor flow properties because of their high interparticle forces. Formulation strategies to improve the flowability of respirable particles include the controlled agglomeration of drug particles and adhesion onto excipient carrier particles in the form of interactive mixtures. The agglomerates or interactive mixtures are required to be strong enough to withstand processing, storage, or transport processes but weak enough to allow drug deaggregation and dispersion during actuation. Controlled agglomeration is obtained by feeding micronized powders through a screw feeder, followed by spheronization in a rotating pan or drum. This method may be used for formulations containing a drug alone (40) or drug-lactose blends (41). Factors affecting the aerosol dispersion of carrier-based formulations include drug and carrier properties such as size, shape, surface roughness, chemical composition and crystalline state, the drug-carrier ratio, and the presence of ternary components.

The drug particle size affects the aerosol dispersion. Different-sized spray-dried mannotol (2.7–7.3 µm) and disodium cromoglycate (2.3–5.2 µm) particles were examined (42,43). Because of less cohesion, higher aerosol dispersion was observed in larger particles; however, lower fine particle fraction (FPF) was produced because of a smaller proportion of fine particles and a greater impact on the throat and upper stages of the impinger. Conditioning or surface modification of drug particles may reduce aggregation and improve aerosol dispersion. The amorphous content of particles may be reduced by treatment with water vapor in controlled temperature and relative humidity conditions (44) or treatment in a vacuum oven (45). Surface modification by adhesion of nanoparticles onto the drug particles may increase aerosol dispersion. Hydrophilic silicic acid and hydroxypropyl methylcellulose phthalate nanoparticles increased device emission and respirable fractions of pranlukast hydrate in both drug-alone and carrier-based formulations (46,47).

Conflicting reports exist on the influence of drug concentration in carrier-based DPI formulations. Increasing drug concentration may increase or reduce the respirable fraction (48–51).

The particle size, shape, surface morphology, and chemical composition of carrier particles can influence aerosol dispersion. Increased drug deposition is generally observed with smaller carrier size (50–53) and increased proportion of fine particles (54,56). However, the carrier size did not affect the FPF in some formulations (56,57). Higher FPF was produced with larger carrier sizes (within 63–90 µm) (49). The use of coarse carrier particles (such as lactose) generally results in increased duration in the airstream drug forces (59). Carriers with smooth surfaces produced higher respirable fractions (59–61). Low-respirable fractions were obtained from carriers with macroscopic surface roughness or smooth surfaces. Higher respirable fractions were obtained from carriers with microscopic surface roughness where smaller contact area and reduced drug adhesion occurred at the tiny surface protrusions (62). A modification of carrier formulation involves the use of soft, friable lactose pellets containing micronized lactose particles, which break down into primary particles during inhalation (63). The drug material may be coated onto the lactose pellets. Carrier particles with good powder flow characteristics exhibited reduced adhesion from a solid surface and produced higher drug deposition (64).

In vitro drug deposition has been examined using different grades of lactose carrier. The higher FPF of salbutamol sulphate obtained from anhydrous and medium lactose was attributed to a higher proportion of fine particles and smooth surface roughness (65). The higher FPF of nacystelyn obtained from anhydrous β-lactose was attributed to its intermediate surface roughness (49). Other sugars were investigated as fine and coarse carriers (66). Higher FPF was obtained using a mannotol coarse carrier, possibly because of a higher fine-particle content and more elongated shape. Mixtures with an added fine-particle carrier produced higher FPF with little difference observed between the fine-carrier type.

The addition of fine ternary components has increased the FPF of various drug particles. Ternary components examined include magnesium stearate, lactose, L-leucine, PEG 6000, and lecithin (48,67–70). Although the mechanism for improved FPF by ternary components has not been fully characterized, possible explanations include the saturation of active sites on the carrier, electrostatic interactions, and drug redistribution on the ternary component.

Recent developments in the improvement of DPI formulation efficiency are focused on particle engineering techniques. Improved aerosol dispersion of particles may be achieved by cospray-drying with excipients such as sodium.
chloride (56) and human serum albumin (HSA) (71). Respirable-sized particles composed of hydrophobic drug and hydrophilic excipients were produced by simultaneous spray-drying of separate solutions through a coaxial nozzle (72). Therapeutically active peptide particles have been produced by spray-drying with good flow and dispersibility properties, including insulin (73), α-1-antitrypsin (74), and β-interferon (75). The addition of stabilizing excipients such as mannitol and HSA generally is required. Spray-dried microspheres composed of cellulose with lower alkyl ethers such as hydroxypropyl methylcellulose may be used for sustained drug release (76). These particles are adhesive following water adsorption from the lung mucosa. Stable dry-powder formulations of polynucleotide complexes were produced by lyophilization with a cryoprotectant such as mannitol followed by sieving or milling (77). A carrier-based formulation of plasmid DNA produced genetic expression in mice following intratracheal insufflation.

Large porous particles (with geometric diameters of 5–30 mm and a tap density less than 0.4 g/mL) with aerodynamic diameters of 1–5 mm are prepared by spray-drying (78,79). These large particles are less cohesive because of reduced van der Waals forces and have improved flow and aerosol dispersion properties. Increased rough surface texture may further minimize particle aggregation and improve flow. Particles deposited in the alveolar regions may avoid phagocytic engulfment by size exclusion. The controlled rate of drug release is achieved using biodegradable polymers such as polyactic acid (PLA) and polyglycolic acid (PGA). Surfactants such as dipalmitoyl phosphatidylcholine may be incorporated to further improve powder flow, aerosol dispersion, and lung deposition (80).

Drug or peptide encapsulated hollow microcapsules are free flowing, easily deaggregated and produce high-respirable fractions. Wall materials include HSA (81) or PGA and PLA (82). Reduced dissolution may be obtained by coating with fatty acids such as palmitic acid (81) or lipid soluble surfactants such as Span 85 (82). The PulmoSphere small, hollow particles (with 5-μm geometric diameters and bulk densities less than 0.1 g/mL) are spray-dried from emulsions of drug, phosphatidylcholine, and perfluorocarbon.

Current commercial DPI formulations are based on drug agglomerates or carrier-based interactive mixtures. Excipients act as diluents and stability enhancers and improve flowability and aerosol dispersibility. Because lactose is the only US-approved excipient for DPI formulations, there is a need for safe alternatives. Suggestions have included carbohydrates such as fructose, glucose, galactose, sucrose, trehalose, raffinose, and melezitose; alditols such as mannitol and xylitol; maltodextrins, dextrose, cyclodextrins, and amino acids such as glycine, arginine, lysine, aspartic acid, and glutamic acid; and peptides such as HSA and gelatin. To mask the unpleasant taste of some inhaled drug compounds, flavoring particles containing maltodextrin and peppermint oil can be incorporated into dry-powder formulations (85). Large-sized particles enhance mouth deposition and reduce lung deposition.

Commercial formulations predominantly deliver bronchodilators, anticholinergics, and corticosteroids for the local treatment of asthma and chronic airway obstruction. New formulations contain multiple drug components such as fluticasone and salmeterol. This causes further complications in the particle interactions involved with powder systems. There has been much speculation on the potential delivery of locally and systemically acting drugs such as analgesics (fentanyl and morphine), antibiotics, peptides (insulin, vasopressin, growth hormone, calcitonin, and parathyroid hormone), RNA/DNA fragments for gene therapy, and vaccines. However, the only new therapy provided using DPI formulations is zanamivir (Relenza, GlaxoSmithKline, Research Triangle Park, NC), which is mainly targeted at the upper respiratory tract for the treatment of influenza.

The use of formulation additives to enhance drug uptake also has been considered. The nature of these absorption promoters is based on a variety of mechanisms, not all of which are fully elucidated. The most well-known are the classical absorption enhancers such as bile salts and surfactants, which are known to disrupt cell membranes and open tight junctions rendering epithelia more permeable (84). This has been followed by the use of small particulates containing drug, which may find their way across epithelia intact. Many of these particulate approaches have yet to be published with respect to lung delivery, but some companies have relevant technology such as Nanosystems, PDC, and BioSante.

An alternative approach involves the close association of a carrier molecule with peptides and proteins for transport across the epithelium (85). The mechanism of improved uptake is not fully characterized for these molecules with respect to the lung epithelium. The maximum doses that can be delivered to the lungs limit the systemic delivery of drugs. However, the potential advantage of all of the particulate or molecular transport promoters is that they may improve the bioavailability of the drug, maximizing the proportion of the dose that reaches the site of action. This is particularly important for macro-molecules, which may not be delivered effectively by any other route of administration (86). The safety implications of using any agent that modifies the physiology of the lung must be fully considered if it is to be adopted for any commercially viable product (87).

Conclusion
Changes in the delivery of inhaled pharmaceuticals come at a time when the po-
The market for compounds to treat potential market is rapidly growing. Self-reported asthma prevalence in the US increased 75% between 1980 and 1994 (88) and to 17.3 million cases in 1998 (89). In children between the ages of 5 and 14, asthma was prevalent in 74.4 children for every 1000 in 1994. Chronic Obstructive Pulmonary Disease (COPD) was the fourth leading cause of death in 1998 with incidence rates of 6.9 per 1000 for all ages and 32.4 per 1000 for ages 65 and over (90). In addition to respiratory therapies, an increasing number of compounds have been suggested for delivery to the lungs as this route of administration becomes better understood. Therapeutic drugs that potentially could be used for lung delivery include antimicrobial agents such as antibiotics and vaccines, proteins such as insulin for diabetes therapy, and nucleic acids or oligonucleotides for cystic fibrosis gene therapy (91–96).

The market for compounds to treat respiratory diseases (e.g., asthma and COPD) is approximately $12 billion worldwide currently and is projected to grow to $20 billion in the next five years (see Figure 6). At present, the DPI share of this market is around 20%. This percentage is likely to grow as pMDIs are slowly phased out and new products are phased in. Compounds intended for systemic delivery represent an even larger potential market. The overall systemic market is projected to be nearly $40 billion during this decade. Clearly, capturing a percentage of this market represents a significant business opportunity for pharmaceutical and delivery systems development companies.

The past couple of years have seen significant consolidation in the pharmaceutical industry. Delivery systems development has participated in this consolidation as device companies have attempted to supplement their technology portfolios or as pharmaceutical companies have purchased an entry into the delivery market. Much of the consolidation in the middle of 2000 was driven by the stock valuations of some of the large capitalizing participants in the market (see Figure 7). Recent volatility in the US equity markets makes it difficult to predict the future direction or the valuations of these companies. As concluded previously, this is a burgeoning field that has yet to reach its full potential. Consequently, it can be expected to experience growth in real terms during the next decade.

References


