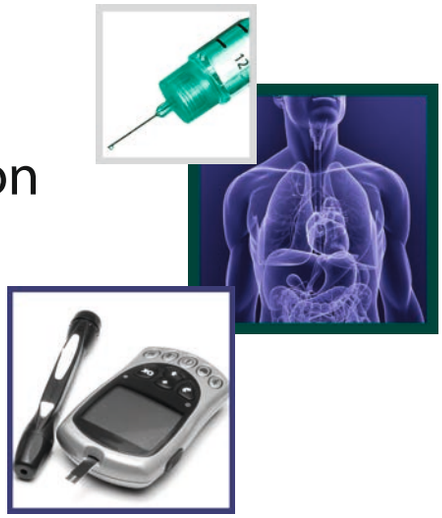
REVIEW

Doctor, stop needling me: an update on alternative routes of insulin administration



Erin D Roe[1], Jason S Woo[2] & Philip Raskin*[3]

Practice Points

- Insulin remains the mainstay treatment for patients with Type 2 diabetes inadequately controlled on oral agents, and all patients with Type 1 diabetes.
- Development of injection-free forms of insulin therapy has been fraught with technical challenges. Few commercial products have reached market entry or achieved sufficient patient adoption.
- The large available surface area and relative lack of immunological barriers generated initial interest in the intrapulmonary route; however, underlying pulmonary physiology produces variable drug absorption. One product, Exubera™, marketed by Pfizer, was withdrawn in 2007; it required ongoing spirometry monitoring and suffered from low adoption.
- Iontophoresis, sonophoresis and flexible 'transferosomes' have been proposed to facilitate drug penetration across the skin, but no method has reached wide-scale clinical testing.
- Intranasal administration requires use of absorption enhancers that may cause mucosal irritation and still fail to produce plasma insulin levels sufficient for treatment.
- Direct insulin delivery to the portal circulation may be more physiologic, reducing weight gain and hypoglycemia.
- Absorption enhancers, encapsulation and molecular modification to enhance lipophilicity, overcome enzyme degradation and facilitate drug absorption.
- Mannkind's Technosphere® inhaled insulin formulation and Generex Oral-lyn™ buccal insulin are two products in late-stage clinical testing, but await regulatory approval in the USA and Europe.
- Overall, technical challenges impede new insulin product development. Conventional insulin therapy, either through intermittent injections or infusion pumps, continue to be primary modalities for treatment of Type 1 and insulin-requiring Type 2 diabetes.

[1]Division of Endocrinology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, G4.100, Dallas, TX 75390-8858, USA
[2]University of Texas Southwestern Medical School, 5323 Harry Hines Blvd, Dallas, TX 75390-9006, USA
[3]Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8858, USA
*Author for correspondence: Tel.: +1 214 648 2017; Fax: +1 214 648 4854; philip.raskin@utsouthwestern.edu

Future Medicine part of fsg

SUMMARY Since its introduction, insulin therapy for diabetes has long been equated with pain, anxiety, lifestyle inconvenience and potential injection-site irritation and lipodystrophy. Efforts to develop noninvasive methods for insulin delivery have relied on molecular modifications, absorption enhancers and encapsulation techniques to resist degradation, promote drug penetration and achieve therapeutic plasma insulin levels. Product development attempts have targeted virtually every mucosal membrane in the body for potential drug delivery. Each administration route has unique physiologic constraints. Potential alternative insulin therapies are discussed with their respective technical challenges. An overview of new drug-delivery platforms currently in development is also provided.

Living a life free from injections is the dream of all patients who require insulin therapy to manage their diabetes. In fact, within a few years of the introduction of insulin, drug development efforts began to focus on alternative routes of administration that avoided subcutaneous injections. However, nearly 100 years later, research continues to focus on modifications to the insulin molecule and drug-delivery platforms that enable noninjectable insulin replacement, minimizing pain and disruption to the patient while simulating the normal physiology of native insulin secretion.

Rates of diabetes in the population continue to grow and disproportionately impact minority populations. Across all age groups, 25.8 million people (8.3% of the population) are diabetic [101]. Among children under the age of 10 years, new cases of Type 1 diabetes exceed Type 2 diabetes (19.7 vs 0.4 cases per 100,000 children); however, this gap narrows for children aged 10–19 years (18.6 vs 8.5 cases, respectively). Higher incidence rates for Type 2 compared with Type 1 diabetes are found in Asian/Pacific Islander and Native American youth, and both non-Hispanic black and Hispanic children have similar incidence rates for Type 1 and Type 2 diabetes. The prevalence of diabetes also increases with age; more than a quarter of US adults over the age of 64 years are diabetic [101]. Data from the CDC also indicates that 72% of patients with diabetes are treated with insulin or a combination of insulin and oral agents [101].

While etiologic factors resulting in Type 1 and Type 2 diabetes differ, the therapeutic intervention for both may include lifelong insulin replacement therapy. In Type 1 diabetes, autoimmune-mediated pancreatic β-cell destruction produces a nonreversible insulin deficiency necessitating exogenous insulin treatment at initial diagnosis. Meanwhile, in Type 2 diabetes, insulin resistance drives hyperinsulinemia which may exceed and eventually deplete β-cell sythetic capacity. When insulin production falls below a critical threshold [1], uncontrolled hyperglycemia manifests first in the postprandial state, and then in the fasting state [2]. While oral agents such as insulin sensitizers (i.e., metformin and thiazolidiones) may maximize remaining endogenous insulin function, and secretogues (i.e., sulfonylurea and nonsulfonylureas) stimulate remaining β-cell reserves, these drugs eventually lose effect and exogenous insulin treatment is required in a subset of patients with Type 2 diabetes. Insulin resistance can be reversed with weight loss through calorie restriction or bariatric surgery. This may obviate the need for exogenous insulin and, in some circumstances, normalize glucose metabolism and 'cure' Type 2 diabetes. More details are emerging on patients who benefit from surgical weight-loss procedures; however, most clinicians continue to advise dietary modification and increased physical activity as first-line therapy to reverse metabolic dysfunction and favorably effect Type 2 diabetes.

Adequate control of Type 1 and Type 2 diabetes is measured by periodic glycosylated hemoglobin levels (HbA_{1c}). The American Diabetes Association (ADA) recommends target levels of less than 7%, which have been shown to reduce the development of long-term diabetic complications [3]. New guidelines published by a joint panel from the ADA and European Association for the Study of Diabetes (EASD) [4] now recommend individualized HbA_{1c} targets that incorporate not only patient-specific factors, such as disease duration, comorbidities, vascular complications and hypoglycemia risk, but also social issues, such as patient resources, social support, attitudes, adherence capability and self-care ability. This latitude enables clinicians to recommend target HbA_{1c} levels that account for individual patient characteristics. More stringent goals of 6.0–6.5% may suit those with short diabetes duration, long life expectancy and no significant vascular complications, while

frail, elderly patients may be better served by HbA_{1c} targets of 7.5–8.0% or even higher [5,6]. Although oral agents are frequently employed in younger patients with shorter disease duration and few complications, their role as add-on or monotherapy in elderly patients is limited due to reduced renal clearance (as with metformin and glyburide) and diminished drug metabolism. It is estimated that up to 25% of elderly patients with Type 2 diabetes receive insulin [7]. Thus, in all patients with Type 1 diabetes and those with Type 2 diabetes requiring insulin, the desire for a pain-free method of insulin administration is particularly acute.

Insulin is a peptide hormone secreted by pancreatic β cells into portal circulation and is extracted by the liver through first-pass metabolism [8,9]. In nondiabetic patients, insulin may be secreted in a low continuous fashion to offset basal hepatic glucose output (HGO) during the fasting state or in larger boluses to meet glycemic excursions following food intake. In the nondiabetic patient, insulin suppresses glucagon release and HGO in the postprandial state. Likewise, glycogenolysis is inhibited and hepatic and peripheral glucose uptake is enhanced by insulin in the postprandial state.

By contrast, patients with Type 1 and Type 2 diabetes possess insufficient endogenous insulin to adequately suppress glucagon release and HGO in the postprandial state. Inadequate HGO suppression may cause hyperglycemia to persist in the fasting state. In the diabetic patient, a lower portal to peripheral insulin concentration gradient (2.5–3-fold lower) [10] is maintained relative to the nondiabetic patent. To restrain hepatic glucose production, supplemental insulin can be given to reproduce the patient's endogenous insulin activity curve with basal and bolus insulin doses that conform to the patient's food intake and lifestyle, while minimizing hypoglycemia risk and weight gain. Supplemental insulin is most commonly delivered through intermittent doses of subcutaneous insulin through multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). CSII is delivered using an insulin pump that provides variable-rate insulin administered into the subcutis.

While oral agents for Type 2 diabetes may only confer a HbA_{1c} decline of 0.5–1.5%, insulin therapy has no dose ceiling and therefore carries greater therapeutic potential. However, insulin treatment may generate concerns of increased hypoglycemia, weight gain, social stigma, lifestyle restriction, injection anxiety, a sense of guilt or failure and a perception of worsening disease, particularly in those with Type 2 diabetes. All of these factors can challenge patient acceptance of insulin therapy [11]. A 2-year compliance study of 6222 adults with insulin-treated Type 2 diabetes found that only 77.44% (standard deviation: 17%) of prescribed insulin was actually administered [12].

New insulin formulations that avoid injection-site pain attract media attention and raise hopes among patients with diabetes and members of the investing community. However, many drug development attempts have been plagued by technical, safety and usability concerns that limit chances of market entry. Because the field continues to evolve, the authors review the characteristics of each administration route and provide an update on the status of current drugs in development.

Alternatives to injectable insulin

■ Inhaled insulin

The first attempts to develop insulin that could be administered noninvasively utilized the intrapulmonary route [13,14], due to its large surface area, thin monolayer of epithelial cells, rich blood supply and relative lack of physical (i.e., mucociliary clearance) or enzymatic barriers. Better aerosol technology and understanding of particulate dispersion in the lung periphery have renewed interest in pulmonary delivery methods [15]. Current platforms employ pressurized metered dose inhalers, dry powder inhalers, nebulizers or aqueous mist inhalers. The bioactivity of inhaled insulin most closely resembles rapid-acting analog insulin, but with slightly prolonged duration making it suitable for postprandial coverage. Its absorption is also influenced by the patient's underlying pulmonary function; smokers may experience increased absorption [16], while those with asthma may have reduced absorption [17,18]. Exercise may also increase inhaled insulin absorption [15]. Furthermore, while pharmacokinetics for inhaled insulin are similar for young and elderly patients, the glucose-lowering effect for the same dose of insulin was lower in elderly patients with Type 2 diabetes, indicating that these patients may require higher treatment doses [19,20]. Therefore, in the case of Exubera™ (Pfizer, Inc., NY, USA), approved for treatment of Type 1 and Type 2 diabetes in January 2006, ongoing and recent smoking was a relative contraindication due to increased hypoglycemia risk,

while unstable or poorly controlled lung disease was an absolute contraindication [21].

Clinical evidence showed that approximately 20–30% of patients using Exubera developed a mild cough that abated with time. The emergence of anti-insulin antibodies [22] was reported, although not felt to signify an adverse immune reaction. Lastly, the insulin produced small, nonprogressive, reversible decreases in lung function [23,24]. While patients reported satisfaction with inhaled insulin, the high cost, particularly in light of its low bioavailability compared with subcutaneous insulin and the need for periodic spirometry, resulted in low market uptake. Exubera was eventually withdrawn from the US market in 2007. Despite this, efforts to develop other inhaled insulins continue. A recent pulmonary safety trial [25] of MannKind's Technosphere® Insulin (TI; Mannkind Corporation, CA, USA) showed initial declines in pulmonary function, including forced expiration volume at 1 s, forced vital capacity and diffusing capacity of carbon monoxide. These changes were nonprogressive after 2-year follow-up and felt not to be clinically significant. No other safety concerns have emerged. Other inhaled insulins currently in development are summarized in **Table 1**. However, it is safe to say that at this point in time, only MannKind continues development of an inhaled insulin formulation.

Transdermal insulin

Several methods have been proposed to enable insulin penetration across the dermis, which is normally impermeable to large hydrophilic molecules, such as insulin. Iontophoresis utilizes low-energy electrical current to enhance skin permeability and drug delivery to subcutaneous tissue [11,26,27]. Although animal studies offer proof-of-concept [28], human studies are still necessary. To achieve consistent plasma insulin concentrations, questions remain to be addressed including methods for removing physical barriers that impede absorption (e.g. hair) and the type of insulin that should be employed [29]. Low-frequency ultrasound (i.e., 'sonophoresis') has also been shown to improve skin permeability [30–33], for insulin contained in an aqueous solution or hydrogel [34]. The treatment duration required to absorb a relatively low insulin dose through a transdermal patch is not sufficient to treat many diabetic patients. Lastly, 'transferosomes' are flexible phosphotidylcholine-based vesicles capable of passing through skin pores. When loaded with insulin, transferosomes have been shown to increase insulin transfer by approximately 50%, reduce blood glucose [12] and deliver a daily dose of basal insulin sufficient to meet the needs of a typical patient with Type 1 diabetes [11,35,36].

Intranasal insulin

Like the lung, the nasal mucosa offers a large epithelial surface area; however, drug absorption is limited by physical barriers, including mucociliary clearance and local proteolytic enzymes. The insulin molecule is also larger than other peptide drugs delivered intranasally (e.g., oxytocin, desmopressin and calcitonin). Insulin's internasal low bioavailability (8–15% [37]) must be increased with absorption enhancers, which in themselves may produce nasal irritation. Although intranasal insulin has been shown to lower blood glucose [38–41], the high doses required, rapid onset and offset of activity [42], and frequent treatment failures make intranasal delivery a nonviable alternative to subcutaneous injections [43].

Oral insulin

Insulin administration via the gastrointestinal tract to portal circulation may act 'more physiologically' on the liver to improve glucose metabolism [44,45]. Using this route, lower doses are needed and peripheral hyperinsulinemia is reduced. Accordingly, oral insulin may reduce risk of weight gain and hypoglycemia associated with conventional subcutaneous insulin treatment [10]. Directed insulin delivery to the portal circulation, such as in islet cell or pancreatic transplantation, is also associated with lower rates of hypoglycemia [46].

Technical challenges in oral insulin development include the timing of administration relative to food intake, unpredictable gastrointestinal transit time, delayed absorption and the effect of food on drug absorption. Oral insulin must also withstand high gastric acidity and enzymatic degradation. Insulin's low bioavailability (~0.5% may reach systemic circulation) in the gastrointestinal tract means that large doses must be used to achieve therapeutic blood levels, and can result in high intra- and inter-subject dosing variability [10].

Recent advances in absorption enhancers, enzyme inhibitors, encapsulated delivery systems and nanoparticles protect insulin from enzymatic degradation. Absorption enhancers, such as surfactants, bile salts, chelating agents

Table 1. Pulmonary insulin delivery platforms.

Company (location)	Technology	Selected clinical data	Development stage
Nektar Therapuetics Inc. (CA, USA) Aventis (NJ, USA) Pfizer (NY, USA)	Nektar Pulmonary Inhaler and Exubera™ dry powder insulin formulation and metered dose inhaler	Studies in patients with DM1 and DM2 vs subcutaneous insulin glargine showed similiar decrease in HbA_{1c}, greater reduction in FBG and PPBG, lower events of hypoglycemia, increased insulin antibody levels and mild decrease in D_{LCO} [62,63]	Product withdrawn from market – October 2007 (low clinical adoption) [102] Increased lung cancer rates reported in certain patient populations – April 2008 [103]
Aradigm Corp. (CA, USA) Novo Nordisk A/S, (Copenhagen, Denmark)	AERx® Insulin Diabetes Management System, liquid aerosol insulin formulation with breath-activated, micro-processor-controlled device	Studies in patients with DM1 and DM2 vs subcutaneous insulin showed similar HbA_{1c}, mildly lower FBG, but similar PPBG [64]. Pulmonary safety assessed [65]	Phase III trials terminated – May 2008 [104] (low presumed clinical benefit compared with injections of analog insulin via pen devices)
Aerogen Inc. (CA, USA)	Aerodose® Inhaler, liquid insulin formulation with breath-activated delivery device	Studies in patients with DM2 showed linear dose–response relationship [66]	Phase II trials terminated – 2003 Aerogen partnered with Dance Pharmaceuticals – January 2011 [105]
Alkermes (MA, USA) Eli Lilly and Co (IN, USA)	AIR™ Pulmonary Delivery System using HIIP® (human inhaled insulin powder), modified insulin-containing particles held in a biodegradable polymer matrix composed of phopholipids [67,68]	Studies of DM1 vs subcutaneous insulin showed similar decreases in HbA_{1c} and PPBG, no difference in hypoglycemic events, greater treatment satisfaction and insulin delivery satisfaction [69,70]	Phase III trials terminated – March 2008 (uncertainties in commercial potential and regulatory enviornment) [104,105]
Mannkind Biopharmaceuticals (NY, USA)	AFREZZA® – Technosphere™ encapsulated insulin in self-assembling microsphere dissolves in neutral pH climate in lung, delivered by Dreamboat™ (a high impedence inhaler) [25,71,72,106]	Studies of DM1 vs subcutaneous insulin showed similar reduction in HbA_{1c}, modest weight decline, fewer hypoglycemic events, similar safety and tolerability [107] Studies of DM2 vs subcutaneous insulin lispro plus basal insulin in both arms showed similar reduction in HbA_{1c}, lower FBG and PPBG, and fewer hypoglycemic events [73]	Phase III trials complete (Additional Phase III trials underway to compare Medtone and Gen2 inhalers, and expand efficacy data in insulin-naive patients) [108]
Abbott Pharmaceuticals, (IL, USA) Formerly Kos Pharmaceuticals (FL, USA)	Dry crystals of recombinant insulin formulation, delivered by propellant-driven handheld BAI	Studies in patients with DM2 vs subcutaneous insulin showed comparable efficacy and safety [74]	Phase IIa trials complete – August 2004 [109] Assume development discontinued – no further information since 2007
Baxter Healthcare Corporation (IL, USA) Formerly Epic Therapeutics (MA, USA)	PROMAXX®, PROtein MAtriX microspheres, dry powder microspheres of recombinant HIIP with administration by dry powder inhalation device (Cyclohaler®)	Studies in healthy patients show safe and efficacious administration of recombinant HIIP with fast onset of action, similar activity to other inhaled insulin formulations [110]	Phase I trial complete – April 2007 [111] Assume development discontinued – no further information since 2007

BAI: Breath actuated inhaler; D_{LCO}: Diffusing capacity of the lung for carbon monoxide; DM1: Diabetes mellitus Type 1; DM2: Diabetes mellitus Type 2; FBG: Fasting blood glucose; HbA_{1c}: Glycated hemoglobin; HIIP: Human insulin inhalation powder; PPBG: Postprandial blood glucose.

and fatty acids, have been tried, but may irritate the intestinal mucosae. Other absorption enhancers rely on covalent modification of the insulin molecule to enhance biostability [47–49]. This technique raises toxicity concerns – both for the unabsorbed insulin and these molecular fragments that, if not degraded by local peptidases and proteases, may be toxic or carcinogenic to cells in the distal gastrointestinal tract [10]. Encapsulation techniques hold insulin within a larger macromolecular 'cage' to protect from degredation [50,51]. Companies with oral and buccal insulin formulations are summarized in **Table 2** [52].

Buccal insulin

Insulin delivered through the buccal mucosa (also included in Table 2) enters systemic circulation, unlike oral insulin. While the buccal membrane contains a relatively large surface area, high vascularity and little proteolytic activity, insulin absorption can be challenged by the multilayered squamous epithelium and variable saliva flow [15]. As with oral insulin, molecular modifications to enhance lipophilicity, as well as absorption enhancers, have been attempted. Enzyme inhibitors, bioadhesive delivery systems and pro-drugs have been used in an attempt to promote absorption. Encapsulation strategies involve using a micelle-like structure to enclose the insulin molecule, which is subsequently aerosolized in a metered dose inhaler [53].

Table 2. Oral and buccal insulin delivery platforms.

Company (location)	Technology	Selected clinical data	Development stage
Oral			
Merrion Pharmaceuticals (Dublin, Ireland) Novo Nordisk A/S, (Copenhagen, Denmark)	GIPET absorption enhancing technology packages insulin (NN1953) in a matrix of medium chain fatty acids (GRAS) to facilitate absorption in the duodenum [112]	No data available to date	Phase II
Biocon Limited (Bangalore, India) Acquired from Nobex Corporation (NC, USA)	Recombinant human insulin (IN-105) conjugated covalently with a monodisperse, short-chain polyethylene glycol derivative that is crystallized and lyophilized into a dry active pharmaceutical ingredient after purification [75], designed to withstand enzymatic degradation and enable gastric absorption	Preliminary studies of DM2 vs placebo showed reductions in HbA_{1c}, PPBG levels and fewer hypoglycemic events [113,114]	Late Phase III, IND filed with the US FDA in December 2009
Diasome Pharmaceuticals, Inc. (PA, USA)	Oral HDV-I, encapsulates insulin in a liposomal structure (≤150 nm in diameter) with a hepatocyte-targeting molecule held in the lipid bilayer. The nano-sized targeting system enables smaller doses of insulin to be utilized	Studies of DM2 vs placebo showed lower PPBG but did not demonstrate dose linearity [76]	Phase II/III – June 2009 No company information since 2009
Diabetology Limited, (St Helier, UK)	Capsulin™, Axcess™ encapsulation-based delivery system utilizes an inert mixture to solubilize and increase absorption in the small intestine	Studies of DM1 vs placebo showed decrease in HbA_{1c}, weight loss and improved triglycerides [115]	Phase IIa completed
Emisphere Technologies, (NY, USA) Novo Nordisk A/S (Copenhagen, Denmark)	Eligen® Technology, utilizes low-molecular-weight carrier molecules that interact weakly and noncovalently with insulin to enhance lipophilicity and GI absorption [51]	Studies of DM2 vs placebo showed decrease of HbA_{1c} and fewer hypoglycemic events [116]	Phase II discontinued (Emisphere to focus on GLP-1 analogs)
Oramed (Jerusalem, Israel)	ORMD-0801, protectant and absorption enhancers to protect insulin through the GI tract [77]	Studies of DM2 vs placebo showed decrease in FBG and HbA_{1c} [117,118]	Phase IIb complete – May 2010
Access Pharmacueticals (TX, USA) bioRASI LLC (Moscow, Russia)	CobOral™, insulin-containing nanoparticles coated with B_{12} analog, (Cobalamin™) utilizes body's natural B_{12} uptake mechanism in the distal ilium [119]	No human studies to date	Preclinical [120,121]
Buccal			
Generex Biotechnology Corporation (ON, Canada)	Oral–Lyn™, rapid-acting insulin encapsulated in micelle, is absorbed through the buccal mucosa using metered dose spray (RapidMist™) device [53,54,122]	Studies of DM1 vs subcutaneous insulin showed similar levels of PPBG, insulin and C-peptide, but prolonged hypoglycemic effects [78] Studies of DM2 vs placebo showed decrease in HbA_{1c}, PPBG levels and increased serum insulin levels [52,79–81]	Approved for use in some countries
Biodel, Inc. (CO, USA)	VIAtab™ proprietary technology temporarily neutralizes peptide hormone-charged surface to allow recombinant human insulin to be absorbed quickly and efficiently on buccal mucosa	Preliminary studies in healthy patients showed safety and positive pharmacokinetic profile [52]	Phase I

DM1: Diabetes mellitus Type 1; DM2: Diabetes mellitus Type 2; FBG: Fasting blood glucose; GI: Gastrointestinal; HbA_{1c}: Glycated hemoglobin; HDV-I: Hepatic-direct vesicle insulin; IND: Investigational new drug application; PPBG: Postprandial blood glucose.

Generex Oral-lyn™ is a recombinant human insulin formulation delivered as a tasteless aerosol mist. A proprietary delivery device (RapidMist™ Diabetes Management System, Generex Biotechnology, ON, Canada) deposits the drug on the buccal mucosa, avoiding spillover to the lung. One spray is equivalent to 10 units of fast-acting insulin analog, of which only 1 unit of insulin is absorbed systemically and appears in circulation within 5–10 min. Clinical testing shows that Oral-lyn is well tolerated. Mild, self-limiting dizziness was the only side effect noted in patients with Type 1 diabetes, while patients with Type 2 diabetes reported no side effects. Oral-lyn's postprandial coverage is equivalent to regular insulin in Type 1 diabetes, and can be used in Type 2 diabetes in patients failing oral agents, in combination with oral agents (metformin and sulfonylurea) or as postprandial insulin in a MDI regimen [54]. The product is currently available in some countries, but awaits regulatory approval in the USA and Europe.

Other routes for insulin delivery

The rectal route has been proposed [55] to circumvent the enzymatic degradation of the gastrointestinal tract and deliver insulin to systemic circulation via lymphatic absorption. The approach is still hindered by low bioavailability (4–10%), variable absorption [15], as well as low perceived acceptability to patients. Intraocular delivery utilizing absorption enhancers has been described in animal studies [56–58] but toxicity concerns have limited subsequent development. Intravaginal delivery, likewise, is limited by low absorption and the potential for severe site reactions [15].

Conclusion

Among diabetic treatments, insulin produces the most potent glucose-lowering effect and durable control of HbA_{1c} levels. However, the inconvenience and discomfort of subcutaneous injections impairs patient adherence and treatment efficacy. The goal of a noninvasive, safe, effective method for insulin delivery has attracted much research and development interest, but few commercial products have entered the market. Only Mannkind's inhaled Technosphere insulin formulation and Generex Oral-lyn buccal insulin continue with later stage clinical testing and development.

Future perspective

While many attempts have been made to deliver insulin noninvasively, ultimately low availability, high cost and unclear clinical benefit compared with conventional subcutaneous insulin have caused these methods to fall out of favor. In its place, research in diabetes therapeutics will continue to strive to replicate normal insulin physiology, perhaps through increasing endogenous insulin secretion via pancreatic or islet cell transplantation [59]. Although still in its early stages, gene therapy [60] has been suggested for adjuvant therapy to enhance glycemic control through GLP-1 receptor stimulation. Finally, antidiabetic vaccines against specific autoantigens, such as insulin, glutamate decarboxylase and heat-shock protein 60, may reduce antibody formation or Type 1 diabetes development in patients with increased genetic susceptibility, or preserve remaining β-cell function in patients who are already diagnosed [61].

Financial & competing interests disclosure

P Raskin has received research support, payable to the University of Texas Southwestern Medical Center, from Andromeda Biotech Ltd, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Calibra Medical Inc., Halozyme Inc., Hoffman-La Roche Inc., Eli Lilly & Company, Osiris Pharmaceuticals Inc., Pfizer Inc, MannKind Corporation, Amylin, Sanofi-aventis, Johnson & Johnson, Takeda and Reata Pharmaceuticals Inc; is an advisor for Amgen, AstraZeneca and Novo Nordisk Inc., and is on the speakers bureau for Novo Nordisk Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Gianani R, Eisenbarth GS. The stages of Type 1A diabetes: *Immunol. Rev.* 204, 232–249 (2005).

2 Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care* 30(2), 263–269 (2007).

3 Standards of medical care in diabetes. *Diabetes Care* 35(Suppl. 1), S11–S63 (2012).

4 Inzucchi SE, Bergenstal RM, Buse JB *et al.* Management of hyperglycemia in Type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 35(6), 1364–1379 (2012).

■■ **Newly updated consensus guidelines for the management of Type 2 diabetes stress a step-wise approach to treatment intensification and individualizing glycemic targets based on patient-specific characteristics.**

5 Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in Type 2 diabetes mellitus: implications of recent clinical trials. *Ann. Intern. Med.* 154(8), 554–559 (2011).

6 Lee SJ, Eng C. Goals of glycemic control in frail older patients with diabetes. *JAMA* 305(13), 1350–1351 (2011).

7 Niskanen L. Insulin treatment in elderly patients with non-insulin-dependent diabetes mellitus. A double-edged sword? *Drugs Aging* 8(3), 183–192 (1996).

8 Eaton RP, Allen RC, Schade DS. Hepatic removal of insulin in normal man: dose response to endogenous insulin secretion. *J. Clin. Endocrinol. Metabol.* 56(6), 1294–1300 (1983).

9 Meistas MT, Rendell M, Margolis S, Kowarski AA. Estimation of the secretion rate of insulin from the urinary excretion rate of C-peptide. Study in obese and diabetic subjects. *Diabetes* 31(5 Pt 1), 449–453 (1982).

10 Arbit E, Kidron M. Oral insulin: the rationale for this approach and current developments. *J. Diabetes Sci. Technol.* 3(3), 562–567 (2009).

11 Cefalu WT. Concept, strategies, and feasibility of noninvasive insulin delivery. *Diabetes Care* 27(1), 239–246 (2004).

■ **Review of alternative modes of insulin administration, including a profile of intrapulmonary insulins in development.**

12 Cramer JA, Pugh MJ. The influence of insulin use on glycemic control: how well do adults follow prescriptions for insulin? *Diabetes Care* 28(1), 78–83 (2005).

13 Gansslen M. Uber Inhalation von insulin. *Klin Wochenschrift* 4, 71 (1925).

14 Von Heubner W, de Jongh SE, Kaquer E. Uber inhalation von insulin. *Klin Wochenschrift* 51, 2342–2343 (1924).

15 Owens DR, Zinman B, Bolli G. Alternative routes of insulin delivery. *Diabetic Med.* 20(11), 886–898 (2003).

16 Himmelmann A, Jendle J, Mellén A, Petersen AH, Dahl UL, Wollmer P. The impact of smoking on inhaled insulin. *Diabetes Care* 26(3), 677–682 (2003).

17 Henry RR, Mudaliar SR, Howland WC 3rd *et al.* Inhaled insulin using the AERx insulin diabetes management system in healthy and asthmatic subjects. *Diabetes Care* 26(3), 764–769 (2003).

18 Morton-Eggleston E, Barrett EJ. Inhaled insulin. *BMJ* 332(7549), 1043–1044 (2006).

19 Henry RR, Mudaliar S, Chu N *et al.* Young and elderly Type 2 diabetic patients inhaling insulin with the AERx insulin diabetes management system: a pharmacokinetic and pharmacodynamic comparison. *J. Clin. Pharmacol.* 43(11), 1228–1234 (2003).

20 Mudaliar S, Henry R, Fryburg D *et al.* Within subject variability of inhaled insulin (Exubera) versus subcutaneous regular insulin in elderly obese patients with Type 2 diabetes mellitus. *Diabetologia* 46(Suppl. 2), A278 (2003).

21 Hollander PA. Evolution of a pulmonary insulin delivery system (Exubera) for patients with diabetes. *Med. Gen. Med.* 9(1), 45 (2007).

22 Fineberg SE, Kawabata T, Finco-Kent D, Liu C, Krasner A. Antibody response to inhaled insulin in patients with Type 1 or Type 2 diabetes. An analysis of initial Phase II and III inhaled insulin (Exubera) trials and a two-year extension trial. *J. Clin. Endocrinol. Metabol.* 90(6), 3287–3294 (2005).

23 Teeter JG, Riese RJ. Dissociation of lung function changes with humoral immunity during inhaled human insulin therapy. *Am. J. Respir. Crit. Care Med.* 173(11), 1194–1200 (2006).

24 Rosenstock J, Cefalu WT, Hollander PA, Klioze SS, Reis J, Duggan WT. Safety and efficacy of inhaled human insulin (Exubera) during discontinuation and readministration of therapy in adults with Type 2 diabetes: a 3-year randomized controlled trial. *Diabetes Technol. Ther.* 11(11), 697–705 (2009).

25 Raskin P, Heller S, Honka M *et al.* Pulmonary function over 2 years in diabetic patients treated with prandial inhaled technosphere insulin or usual antidiabetes treatment: a randomized trial. *Diabetes Obes. Metabol.* 14(2), 163–173 (2012).

26 Sage BH Jr. Insulin iontophoresis. *Pharm. Biotechnol.* 10, 319–341 (1997).

27 Chien YW, Siddiqui O, Sun Y, Shi WM, Liu JC. Transdermal iontophoretic delivery of therapeutic peptides/proteins. I: insulin. *Ann. NY Acad. Sci.* 507, 32–51 (1987).

28 Kanikkannan N, Singh J, Ramarao P. Transdermal iontophoretic delivery of bovine insulin and monomeric human insulin analogue. *J. Control Release* 59(1), 99–105 (1999).

29 Langkjaer L, Brange J, Grodsky GM, Guy RH. Iontophoresis of monomeric insulin analogues *in vitro*: effects of insulin charge and skin pretreatment. *J. Control Release* 51(1), 47–56 (1998).

30 Tachibana K. Transdermal delivery of insulin to alloxan-diabetic rabbits by ultrasound exposure. *Pharm. Res.* 9(7), 952–954 (1992).

31 Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. *Science* 269(5225), 850–853 (1995).

32 Mitragotri S. Healing sound: the use of ultrasound in drug delivery and other therapeutic applications. *Nat. Rev. Drug Discov.* 4(3), 255–260 (2005).

33 Boucaud A, Garrigue MA, Machet L, Vaillant L, Patat F. Effect of sonication parameters on transdermal delivery of insulin to hairless rats. *J. Control Release* 81(1–2), 113–119 (2002).

34 Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. *Nat. Rev.* 3(2), 115–124 (2004).

35 King MJ, Badea I, Solomon J, Kumar P, Gaspar KJ, Foldvari M. Transdermal delivery of insulin from a novel biphasic lipid system in diabetic rats. *Diabetes Technol. Ther.* 4(4), 479–488 (2002).

36 Cevc G. Transdermal drug delivery of insulin with ultradeformable carriers. *Clin. Pharmacokinet.* 42(5), 461–474 (2003).

37 Frauman AG, Jerums G, Louis WJ. Effects of intranasal insulin in non-obese Type II diabetics. *Diabetes Res. Clin. Pract.* 3(4), 197–202 (1987).

38 Salzman R, Manson JE, Griffing GT *et al.* Intranasal aerosolized insulin. Mixed-meal studies and long-term use in Type I diabetes. *N. Engl. J. Med.* 312(17), 1078–1084 (1985).

39 Coates PA, Ismail IS, Luzio SD *et al.* Intranasal insulin: the effects of three dose regimens on postprandial glycaemic profiles in Type II diabetic subjects. *Diabetic Med.* 12(3), 235–239 (1995).

40 Lalej-Bennis D, Boillot J, Bardin C *et al.* Six month administration of gelified intranasal insulin in 16 Type 1 diabetic patients under multiple injections: efficacy vs subcutaneous injections and local tolerance. *Diabetes Metabol.* 27(3), 372–377 (2001).

41 Lalej-Bennis D, Boillot J, Bardin C *et al.* Efficacy and tolerance of intranasal insulin administered during 4 months in severely hyperglycaemic Type 2 diabetic patients with oral drug failure: a cross-over study. *Diabetic Med.* 18(8), 614–618 (2001).

42 Bruce DG, Chisholm DJ, Storlien LH, Borkman M, Kraegen EW. Meal-time intranasal insulin delivery in Type 2 diabetes. *Diabetic Med.* 8(4), 366–370 (1991).

43 Hilsted J, Madsbad S, Hvidberg A *et al.* Intranasal insulin therapy: the clinical realities. *Diabetologia* 38(6), 680–684 (1995).

44 Satake S, Moore MC, Igawa K *et al.* Direct and indirect effects of insulin on glucose uptake and storage by the liver. *Diabetes* 51(6), 1663–1671 (2002).

45 Shishko PI, Kovalev PA, Goncharov VG, Zajarny IU. Comparison of peripheral and portal (via the umbilical vein) routes of insulin infusion in IDDM patients. *Diabetes* 41(9), 1042–1049 (1992).

46 Ryan EA, Shandro T, Green K *et al.* Assessment of the severity of hypoglycemia and glycemic lability in Type 1 diabetic subjects undergoing islet transplantation. *Diabetes* 53(4), 955–962 (2004).

47 Still JG. Development of oral insulin: progress and current status. *Diabetes Metabol. Res. Rev.* 18, S29–S37 (2002).

48 Kipnes M, Dandona P, Tripathy D, Still JG, Kosutic G. Control of postprandial plasma glucose by an oral insulin product (HIM2) in patients with Type 2 diabetes. *Diabetes Care* 26(2), 421–426 (2003).

49 Clement S, Still JG, Kosutic G, McAllister RG. Oral insulin product hexyl-insulin monoconjugate 2 (HIM2) in Type 1 diabetes mellitus: the glucose stabilization effects of HIM2. *Diabetes Technol. Ther.* 4(4), 459–466 (2002).

50 Katpitza C, Arbit E, Abbas R *et al.* Oral insulin: proof of concept in Type 2 diabetes patients. *Diabetologia* 46(Suppl. 2), Abstract 8 (2003).

51 Kidron M, Dinh S, Menachem Y *et al.* A novel per-oral insulin formulation: proof of concept study in non-diabetic subjects. *Diabetic Med.* 21(4), 354–357 (2004).

52 Heinemann L, Jacques Y. Oral insulin and buccal insulin: a critical reappraisal. *J. Diabetes Sci. Technol.* 3(3), 568–584 (2009).

■ **Review of the physiology and pharmacology of oral insulin delivery and the companies with candidate agents currently in development.**

53 Palermo A, Napoli N, Manfrini S, Lauria A, Strollo R, Pozzilli P. Buccal spray insulin in subjects with impaired glucose tolerance: the prevoral study. *Diabetes Obes. Metabol.* 13(1), 42–46 (2011).

54 Pozzilli P, Raskin P, Parkin CG. Review of clinical trials: update on oral insulin spray formulation. *Diabetes Obes. Metabol.* 12(2), 91–96 (2010).

55 Ritschel WA, Ritschel GB. Rectal administration of insulin. *Methods Find. Exp. Clin. Pharmacol.* 6(9), 513–529 (1984).

56 Xuan B, McClellan DA, Moore R, Chiou GC. Alternative delivery of insulin via eye drops. *Diabetes Technol. Ther.* 7(5), 695–698 (2005).

57 Morgan RV, Huntzicker MA. Delivery of systemic regular insulin via the ocular route in dogs. *J. Ocul. Pharmacol. Ther.* 12(4), 515–526 (1996).

58 Lee Y, Yalkowsky SH. Systemic absorption of insulin from a Gelfoam ocular device. *Int. J. Pharm.* 190(1), 35–40 (1999).

59 Richter A, Lerner SM. Schroppel B. Curing diabetes with transplantation? *Mount Sinai J. Med.* 79(2), 267–275 (2012).

60 Riedel MJ, Kieffer TJ. Treatment of diabetes with glucagon-like peptide-1 gene therapy. *Expert Opin. Biol. Ther.* 10(12), 1681–1692 (2010).

61 Plotkin SA. Vaccines: correlates of vaccine-induced immunity. *Clin. Infect. Dis.* 47(3), 401–409 (2008).

62 Quattrin T, Bélanger A, Bohannon NJ, Schwartz SL; Exubera Phase III Study Group. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with Type 1 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 27(11), 2622–2627 (2004).

63 Hollander PA, Blonde L, Rowe R *et al.* Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with Type 2 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 27(10), 2356–2362 (2004).

64 de Galan BE, Simsek S, Tack CJ, Heine RJ. Efficacy and safety of inhaled insulin in the treatment of diabetes mellitus. *Netherlands J. Med.* 64(9), 319–325 (2006).

65 Hermansen K, Rönnemaa T, Petersen AH, Bellaire S, Adamson U. Intensive therapy with inhaled insulin via the AERx insulin diabetes management system: a 12-week proof-of-concept trial in patients with Type 2 diabetes. *Diabetes Care* 27(1), 162–167 (2004).

66 Kim D, Mudaliar S, Chinnapongse S *et al.* Dose-response relationships of inhaled insulin delivered via the Aerodose insulin inhaler and subcutaneously injected insulin in patients with Type 2 diabetes. *Diabetes Care* 26(10), 2842–2847 (2003).

67 Edwards DA, Hanes J, Caponetti G *et al.* Large porous particles for pulmonary drug delivery. *Science* 276(5320), 1868–1871 (1997).

68 Edwards DA, Ben-Jebria A, Langer R. Recent advances in pulmonary drug delivery using large, porous inhaled particles. *J. Appl. Physiol.* 85(2), 379–385 (1998).

69 Garg S, Rosenstock J, Silverman BL *et al.* Efficacy and safety of preprandial human insulin inhalation powder versus injectable insulin in patients with Type 1 diabetes. *Diabetologia* 49(5), 891–899 (2006).

70 Muchmore DB, Silverman B, De La Peña A, Tobian J. The AIR inhaled insulin system: system components and pharmacokinetic/glucodynamic data. *Diabetes Technol. Ther.* 9(Suppl. 1), S41–S47 (2007).

71 Pfutzner A, Mann AE, Steiner SS. Technosphere/Insulin – a new approach for effective delivery of human insulin via the pulmonary route. *Diabetes Technol. Ther.* 4(5), 589–594 (2002).

72 Kapsner P, Bergenstal RM, Rendell M *et al.* Comparative efficacy and safety of Technosphere insulin and a rapid-acting analog both given with glargine in subjects with T1DM in a 52-week study. *Diabetologia* 52(Suppl. 1), Abstract 982 (2009).

■ **Efficacy and safety review of a promising oral insulin drug, Afrezza®.**

73 Rosenstock J, Lorber DL, Gnudi L *et al.* Prandial inhaled insulin plus basal insulin glargine versus twice daily biaspart insulin for Type 2 diabetes: a multicentre randomised trial. *Lancet* 375(9733), 2244–2253 (2010).

74 Hausmann M, Dellweg S, Heinemann L, Buchwald A, Heise T. Add-on therapy with Kos inhaled insulin is as efficacious as add-on therapy with Lantus in poorly controlled Type 2 diabetic patients treated with sulfonylureas or metformin. Presented at: *The European Association for the Study of Diabetes 41st Annual Meeting.* Athens, Greece, 12–15 September 2005 (Abstract 817).

75 Dave N, Hazra P, Khedkar A, Manjunath HS, Iyer H, Suryanarayanan S. Process and purification for manufacture of a modified insulin intended for oral delivery. *J. Chromatogr. A.* 1177(2), 282–286 (2008).

76 Iyer H, Khedkar A. Verma M. Oral insulin – a review of current status. *Diabetes Obes. Metabol.* 12(3), 179–185 (2010).

■■ **Review of oral insulin medication with pharmacokinetic and pharmacodynamics information.**

77 Kidron M, Raz IM, Wolfenberger M, Schwob H, Schruefer C. Pharmacokinetics (PK) and pharmacodynamics (PD) of oral insulin in healthy subjects. Presented at: *68th Annual Meeting, American Diabetes Association.* San Francisco, CA, USA, 6–8 June 2008.

78 Guevara-Aguirre J, Guevara-Aguirre M, Saavedra J, Bernstein G, Rosenbloom AL. Comparison of oral insulin spray and subcutaneous regular insulin at mealtime in

Type 1 diabetes. *Diabetes Technol. Ther.* 9(4), 372–376 (2007).

79 Bernstein G. Delivery of insulin to the buccal mucosa utilizing the RapidMist system. *Expert Opin. Drug Deliv.* 5(9), 1047–1055 (2008).

80 Annabestani Z, Sharghi1 S, Shahbazi S *et al.* Insulin buccal spray (Oral-Lyn) efficacy in Type 1 diabetes. *Iranian J. Diabetes Lipid Disord.* 9(18), (2010).

81 Guevara-Aguirre J, Guevara M, Saavedra J, Mihic M, Modi P. Oral spray insulin in treatment of Type 2 diabetes: a comparison of efficacy of the oral spray insulin (Oralin) with subcutaneous (SC) insulin injection, a proof of concept study. *Diabetes Metabol. Res. Rev.* 20(6), 472–478 (2004).

■ Websites

101 National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States. CDC (Ed.). US Department of Health and Human Services, Atlanta, GA, USA (2011). www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf
(Accessed 20 April 2012)

102 Pfizer and Nektar reach agreement on Exubera®.
www.pfizer.com/news/press_releases/pfizer_press_release_archive.jsp?guid=20071113005860en&source=RSS_2007&page=1
(Accessed 20 April 2012)

103 Pfizer statement on Exubera labeling update in the United States.
www.pfizer.com/news/press_releases/pfizer_press_release_archive.jsp?guid=20080409005647en&source=RSS_2008&page=10
(Accessed 20 April 2012)

■ **Pfizer statement regarding Exubera® market withdrawal.**

104 EdgarOnline. Competition/competitors 2012.
http://ipo.nasdaq.com/TextSection.asp?cikid=9398&fnid=52795&sec=cm
(Accessed 12 April 2012)

105 Aerogen partner with Dance Pharmaceuticals.
www.aerogen.com/news/9/82/Aerogen-Partner-with-Dance-Pharmaceuticals.html
(Accessed 18 April 2012)

106 AFREZZA® – a novel ultra rapid-acting insulin.
www.mannkindcorp.com/product-pipeline-diabetes-afrezza.htm
(Accessed 14 April 2012)

107 Type 1 diabetes patients using AFREZZA have more positive view of therapy compared to standard insulin therapy.
www.news.mannkindcorp.com/phoenix.zhtml?c=147953&p=irol-newsArticle&ID=1579722&highlight=
(Accessed 18 April 2012)

■ **Mannkind Corporation's Afrezza® product information and comparative data results.**

108 MannKind fights on with its diabetes game-changer Afrezza.
http://seekingalpha.com/article/704841-mannkind-fights-on-with-its-diabetes-game-changer-afrezza
(Accessed 18 April 2012)

109 Jones D. Abbott: no lung-cancer signals in inhaled-insulin trials 2008 (2012).
www.natap.org/2008/newsUpdates/041108_03.htm
(Accessed 20 April 2012)

110 Findings suggest insulin powder produced using Baxter's PROMAXX microsphere technology was absorbed systemically with no reported cough or shortness of breath.
www.baxter.com/press_room/press_releases/2007/04-20-07-promaxx.htm
(Accessed 20 April 2012)

111 Inhaled insulin study moves ahead.
www.bio-medicine.org/medicine-news/Inhaled-Insulin-Study-Moves-Ahead-20195-1
(Accessed 20 April 2012)

112 Merrion Pharmaceuticals (2012). Novo Nordisk A/S successfully completes single dose Phase I trial oral insulin (NN1953) using merrion pharmaceuticals GIPET® technology.
www.merrionpharma.com/content/investors/archive/030212.asp
(Accessed 7 April 2012)

113 Anant H. Biocon releases preliminary data on IN-105 oral insulin, in pharma age (2011).
www.biocon.com/docs/PR_100111.pdf
(Accessed 17 April 2012)

■ **Study data regarding potential oral insulin drug, IN-105.**

114 Morrison N. Biocon close to finalizing partnership for development of oral insulin.
www.in-pharmatechnologist.com/Ingredients/Biocon-close-to-finalising-partnership-for-development-of-oral-insulin
(Accessed 13 April 2012)

115 Diabetology. Oral Insulin.
www.diabetology.co.uk/oral.htm
(Accessed 16 April 2012)

116 Emisphere. Emisphere reports additional clinical data from Phase II oral insulin trial.
http://ir.emisphere.com/releasedetail.cfm?ReleaseID=356380
(Accessed 15 April 2012)

117 Eyers P. Diabetes therapies & diagnostics: Global Markets HLC029C, in BCC Research (2010).
www.bccresearch.com/report/diabetes-therapies-diagnostics-hlc029c.html
(Accessed 18 April 2012)

118 Oramed.
www.oramed.com/index.php?page=14
(Accessed 12 April 2012)

119 Cobalamin™ – mediated oral drug delivery. Access Pharmaceuticals
www.accesspharma.com/product-programs/cobalamin-mediated-oral-drug-delivery
(Accessed 12 April 2012)

120 Zeng G. Access Pharma. Zacks small-cap research.
www.accesspharma.com/downloads/analyst-reports/ACCP-Zacks-4.pdf
(Accessed 17 April 2012)

121 Access Pharmaceuticals. Investor presentation Q1 (2011).
www.accesspharma.com/downloads/investor-relations/ACCP-Corporate-Presentation.pptx
(Accessed 15 April 2012)

122 Generex Biotechnology Corporation.
http://generexind.com/researcharchive.html
(Accessed 15 April 2012)