

# Dutch pacemakers: a Groningen invention, turned by Vitatron into many ground breaking innovations

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## Summary

On March 21<sup>st</sup>, 1962<sup>2</sup>, a team led by Dr J.W. van den Berg, professor at the Laboratory of Medical Physics, Groningen University, successfully implanted a permanent cardiac pacemaker in a male patient. Since 1960, building on the results of many others including Zoll<sup>3</sup>, Furman<sup>4</sup> and Senning<sup>5</sup>, the Groningen team had developed a transistorised, two-gear pacemaker. After extensive testing, the device became available for clinical and routine applications at the Groningen University hospital.

The Laboratory, which produced the devices, however, was unable to provide sufficient units to meet growing patient demands. Van den Berg thus had to source an outside producer.

A year after the successful Groningen implantation, in July 1963, the Dutch company Vitatron took over the production of pacemakers and established a dedicated factory in Dieren. It became a fruitful and lasting cooperation between research, clinic and industry.

In the following 20+ years, the company spearheaded many new developments - including the world's first microprocessor based pacemaker in 1981. Vitatron's R&D led to a series of high-tech innovations in pacemakers and patents, tools and supporting instruments. By March 1986, in need of additional funding to support on-going technical and marketing activities, the company was bought by the American medical device giant Medtronic. Rather than being renamed or fully absorbed by its buyers, Vitatron continued as an independent brand name.<sup>6,7</sup>

This article covers Vitatron's pacemaker activities during its Dutch ownership until Q1 1968.

## Introduction

### 1962- The pacemaker from Groningen

By 1960, Professor Homan van de Heide<sup>8</sup> and his mentor Dr Eerland, both thoracic surgeons at the Surgical Clinic Groningen, were seeking improvements to existing pacemakers beyond those that were developed by Senning and Elmqvist. Van de Heide's objective was to achieve long-term independent artificial pacing of the human heart by means of an implanted pulse generator.

They approached Professor van den Berg of the Laboratory of Medical Physics, Groningen University. Van den Berg extensively studied various ways to operate a pulse generator, to evaluate the mechanical stability and reliability to connect an electrode with the heart. In

addition, he designed various energy-efficient electronic circuits to drive the pulse generator.

After a series of implantations of pacemakers in dogs, the team reported its first successful clinical application on March 21<sup>st</sup>, 1962<sup>9</sup>. Key components in Van den Berg's implantation were a transistorised, 2-gear<sup>10</sup> pacemaker, powered by 6 mercury-zinc batteries.<sup>11</sup> The pacemaker<sup>12</sup> transmitted its pulses via a stainless steel wire to platinum pin electrodes. These pins were 'stung' into the heart.<sup>13</sup> The pacemaker itself was embedded in an epoxy resin, fully encapsulated in a soft, silicone rubber.

By April 1963, the student-assistant Hilbert Thalen joined van den Berg's team to further improve and develop the Groningen results. Thalen grew to become the leader in the project, while being extensively engaged in further developments of the initial pacemaker and its successors.<sup>14,15</sup> Following successes with a growing number of patients at the Groningen University, demands for the pacemaker increased significantly. As the Groningen Laboratory itself would not be able to produce pacemakers in sufficient numbers, van den Berg<sup>16</sup> contacted the company Vitatron in Amsterdam, to assist in the production and administration of pacemakers.

### From Groningen to Dieren

#### 1963 - Vitatron's production for a larger market

In July 1963, Vitatron<sup>17</sup> took up series production<sup>18</sup> of the PM 100 pacemaker in Dieren, some 150 km south of Groningen. Initially, the company built the same device as was designed and produced by the Laboratory (Fig. 1). Van den Berg and Thalen<sup>19,20</sup> both became scientific advisors to Vitatron.<sup>21</sup>

Two years later, after numerous implanted pacemakers, ongoing clinical expertise was incorporated into a new Vitatron pacemaker design, the MIP-100<sup>22</sup> (Fig. 2) together with an intramural pacemaker electrode, the MIP-120.<sup>23</sup> Also extensive support equipment was developed such as a device to monitor the pacemaker, both before and during the implantation<sup>24</sup> in the patient. Other tools developed by Vitatron ensured the interconnectivity between its own pacemakers or electrodes and those constructed by other manufacturers. By June 1966, the MIP-100 was also launched in the USA.<sup>25</sup> Vitatron felt ready to conquer the world.<sup>26</sup>

From the onset of its production, each Vitatron pacemaker<sup>27</sup> was designed to operate at a fixed rate and in an asynchronous mode: a pulse generator, using an electrode (lead),



Fig. 1 V34040 - Early series Vitatron pacemaker PM 100, 1963 - 1965, fully sealed, 2 leads. Please note the one Euro coin is for size reference only.



Fig. 2 V34036 - MIP-100 - 'Groningen' pacemaker, fixed, dual heart rate, 1965 onwards, single (-) lead / (+) plate.

paces (fires) at a fixed frequency; no feedback function - i.e. no sensing of any existing, intrinsic cardiac activity is being performed.

By the mid-60s, various companies started to implement a second basic pacemaker concept: apart from the fixed rate device, the concept of 'non-competitive' pacing (later known as 'on demand' or simply 'demand') was introduced. This approach would either be implemented as 'inhibited' or as 'triggered'. Vitatron, following Thalen's thesis<sup>28</sup>, choose for the 'inhibited' version: if the heart does not fire on its own, the pacemaker senses this and paces the heart at a fixed rate; if, however, the heart does resume its own cardiac rhythm, the pacemaker also senses this but *suspends* its

artificial paced rhythm, thus saving energy from the device batteries.

By 1969, 6 years after the production of a single type pacemaker, Vitatron had developed a portfolio of medical technology and was able to offer a range of asynchronous pacemakers, including a standard-, a high power- and a children version. In addition, the company offered a 'demand' pacemaker<sup>29</sup> and a suite of supporting devices.<sup>30</sup>

To broaden the scope of its activities along the lines of Seymour Furman, Vitatron had also developed a series of *intracardiac* electrodes to connect the pulse generator with the heart. As with van den Berg's first generation of pacemakers, the initial electrode would be connected to the *outside* (e.g. intramural) of the heart. In the new approach, the lead would be positioned from *within* the heart.<sup>31</sup> This type of intracardiac leads, with a range of stiffness and tip configuration, would be implemented by inserting the lead as a catheter through the vein into the heart.

As with other manufacturers, Vitatron was not without its production challenges. When asked to comment on its pacemaker reliability, Thalen noted that between 1962 and 1966 about 50% (!) of its implanted pacemakers had become defective, requiring to be - surgical intervention- replaced. When making changes to the composition of the epoxy that was used, issues were greatly solved.<sup>32,33</sup>

## Improved Mercury-Zinc Powered Pacemakers

### 1972 - Ensuring quality products

By early 1972<sup>34</sup>, Vitatron released a new series of pacemakers.<sup>35</sup> While material, size and shape were similar to the previous mercury-zinc powered pacemakers, Vitatron had fully overhauled the inside of its pacemakers. It wanted to ensure that these devices would indeed meet a much higher degree of reliability: new pacemakers were offered with a 30 months / 100% guarantee.<sup>36</sup> Experiences in the production process gained in previous pacemakers were also incorporated. Electronics design was greatly enhanced, now using high-end<sup>37</sup> components. Compared to previous series, which did include magnetic switches, transistors were now applied to automatically shift back and forth between the 'fixed rate' and 'demand' function<sup>38</sup> of the pacemaker.

From the perspective of a cardiologist, who would routinely see his patient, the pacemaker functionality was also improved: once im-



Fig. 3 V33064 - MIP-42 'Demand' pacemaker 0.5 ms, 70 bpm, 1976–1979.

planted, key parameters of the device could be checked during a routine patient control using Vitatron's VCA<sup>39</sup> technology. This would no longer require surgical intervention.

These improved mercury-zinc pacemakers were produced between 1972 and 1979. Over 90% of these series<sup>40</sup> were of type 'demand', MIP-40/42/43 units (Fig. 3). The remaining units were 'fixed rate' devices.

In a briefing note of 1978, Vitatron claimed to offer extremely reliable products: '...we base this statement on more than 15 years of experience in the design and manufacture of pulse generators, leads and analysis equipment...'

## Lithium Batteries

### 1967 - Help from outside

Since the start of Vitatron's pacemakers<sup>41</sup>, mercury-zinc batteries were the sole power source to all its devices. By 1967<sup>42</sup> Catalyst Research Corporation (CRC), a small Baltimore battery manufacturer, had invented a battery cell with a lithium anode / iodine cathode. The company, however, had problems in finding commercial use for it. When CRC contacted Wilson Greatbatch<sup>43</sup>, he immediately understood the much wider implications of lithium as a power source for pacemakers. By 1973, Greatbatch started his own company (WGL), producing lithium batteries based on the CRC design. The high energy density of lithium enabled manufacturers to significantly downsize their pulse generators. Moreover, this type of battery does not generate gas or self-discharge reactions as a by-product. At last, the entire lithium powered pulse generator could therefore be hermetically sealed. Greatbatch had thus almost single-handedly turned the global pacemaker industry from

mercury-zinc to lithium.<sup>44</sup>

## New Steps: CPS

### 1979 - Half in volume and half in weight, lifetime increased triple or more

When Vitatron in 1976 released the series CPS<sup>45</sup> pacemakers, it had banked heavily on new opportunities of the lithium battery technology. The much higher density of these batteries, the ability to downsize pulse generators together with a significantly longer lifetime enabled a number of opportunities to improve on its technology. Vitatron introduced various types of lithium batteries<sup>46</sup> and combined these with some other important step-by-step improvements:

- Now that the mercury-zinc battery releases hydrogen - requiring it to be vented into the body tissue - was no longer an issue, the pacemaker housing question could be solved. In a highly sophisticated manner, Vitatron developed a technique where two parts of a titanium case (only) could be hermetically sealed, using a laser welding procedure in a pure plasma atmosphere.
- The electronics of the first CPS versions were developed and produced using individual elements. In later series, via partly-integrated and planar film using monolithic Integrated Injection Logic (I<sup>2</sup>L) technology, analogue and digital functions could be combined into single chips.<sup>47,48</sup> Stanford University assisted Vitatron to integrate part of the pacemaker and the chip. By September 1979, Vitatron was able to produce its own 'flat pack' chips, produced by Vitatron's subsidiary Vitarel in San Diego, USA.<sup>49</sup>
- The first CPS series pacemakers continued to use Vitatron's VCA approach, routinely checking the pacemaker functionality while implanted. Later series included new developments to select and validate key pacemaker parameter settings such as amplitude output and pacing rates.<sup>50</sup> Using a simple movement of a standard magnet above the patient and an ECG recorder, in a 'step-down' approach, these two parameters became programmable after being implanted. By selecting the *lowest* possible pacing pulse amplitude, while again using an ECG recorder, the lifetime of the pacemaker is further extended.<sup>51</sup>

Comparing the improved mercury-zinc pulse generators with those in the CPS series, Vitatron had achieved - within a few years - that their pacemakers had become *half* in volume and *half* in weight, while the lifetime had *in-*

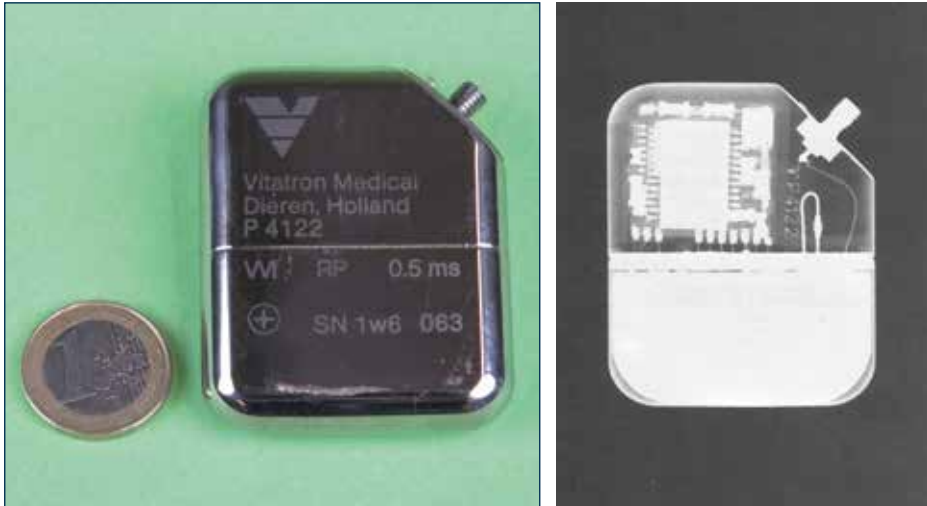


Fig. 4 (a) V34052 - P4122 'Demand' pacemaker, titanium casing, Vitatron's first single chip, 1978 onwards; (4b) x-ray of same.

created triple or more. Moreover, Vitatron had arrived to produce a (re-) programmable pacemaker, all in a single chip<sup>52</sup> (Fig. 4a/b).

In parallel to the developments of its pacemaker technology, Vitatron also made significant improvements in its lead technology. In 1975, Thalen patented a Low Output Electrode. This endocardial lead - through its small stimulation surface- could significantly extend the lifetime of the pulse generation. Another improvement was the *Helifix* endocardial lead, released in 1978. Vitatron's most successful lead consists of a rather unique spiral shaped lead that can be anchored by two or three clockwise turns (Fig. 5a/b).

### From Hardwired- to Software Pacemakers

#### 1981 - The world first microprocessor-based pacemaker

So far, all pacemakers were implemented as hardwired electronic circuits, either built as individual electronic parts such as the MIP-100, or much later, as a single, partly analogue / partly digital chip such as the P-4122 pacemaker.

In 1981, Vitatron launched the world's first

microprocessor-based pacemaker<sup>53</sup>, the diagnostic pulse generator **Quintech DPG**. The introduction of a software-based pacemaker, using a microprocessor, enabled flexibility to introduce and modify a range of parameters and algorithms. Electrical input signals would be converted from analogue to digital signals. Next, extensive information about spontaneous cardiac activity would be fed into specific algorithms and converted back into advanced pacing schemes to control the heart rate.

Before this could be achieved, Vitatron had to undertake extensive developments to create a new technological environment. It also had to extensively train staff, surrounded by significant financial investments, before the company would be ready to move from hardwired - to software pacemakers. On top of that, Vitatron had to guarantee that software solutions would be at least as reliable as (previous) hardwired versions. Furthermore, the company had to ensure that a universal programming system for future Vitatron pacemakers would be available.

The Quintech DPG (Fig. 6) pacemaker consists of a series of selectable pacing algorithms and analysis tools. When in program-

ming mode, the pacemaker can either be implemented as 'demand' or 'fixed' version, in either ventricle- or atrium mode<sup>54</sup> with a selectable range of stimulation frequencies, output amplitude and refraction periods. These parameters were now software-selectable rather than hardwired solutions.

The analysis part of the pacemaker collects and stores numerical results inside the device such as Holter functions<sup>55</sup> to generate heart rate histograms and arrhythmia counters.<sup>56</sup> In addition, device parameter status such as stimulation threshold, lead - and battery impedance can be measured. Whereas in hardwired pacemakers, those parameters would at most only be available *during* the medical implantation of the pacemaker, in the microprocessor-based pacemaker, these results were now routinely stored inside the pacemaker and available whenever required.

A two-way digital communication between the implanted Quintech DPG pacemaker and a desk computer HP-85<sup>57</sup> personal computer is ensured via a Vitatron medical programmer head, using dedicated communication software.<sup>58</sup> A cardiologist, supervising his patient, immediately receives a series of selectable diagnostics and can adjust his therapy on bases of long-term heart frequency data and select special pacing modes such as flywheel or overdrive.<sup>59</sup>

### Rate Responsive Pacemakers

#### 1982 - Metabolic demands

A conventional pacemaker, such as the ventricular inhibited pacemaker, carries with it the disadvantage of pacing at a *fixed* rate.<sup>60</sup> The device does not increase its rate in response to metabolic demand, as it is not designed to respond to this 'event'. In an effort to determine an optimal pacing rate, various investigators began to look for indicators of *metabolic*<sup>61</sup> demand.

One of the areas under investigation has been the QT interval<sup>62</sup> of the QRS complex. In 1979, Rickards<sup>63</sup> showed that at fixed paced rates, the QT interval changed during exercise

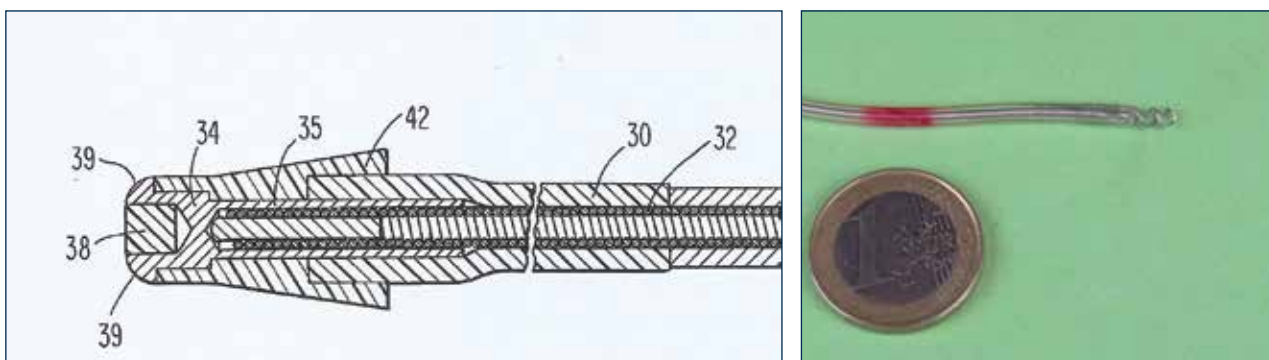


Fig. 5 (a) Thalen's Low Output Electrode: part drawing from USA Patent 4,030,508: 38 - non-conductive, 39 - conductive, round 2,7 mm; (b) V33004 - Helifix endocardial lead, 1978.



Fig. 6 V33076 - *Quintech DPG* - diagnostic pulse generator; world's first microprocessor based pacemaker (model 921), 1981 onwards.



Fig. 7 V32996 - *Quintech TX*, Rate Response pacemaker, 1982 onwards.

and during emotional stress due to increased levels of catecholamines. This physiological phenomenon could therefore be used to develop a rate-responsive pacemaker.<sup>64</sup>

After a series of clinical trials, in 1982, Vitatron<sup>65</sup> introduced the **Quintech TX**<sup>66</sup>, the first rate responsive pacemaker based on a QT sensing circuit. The algorithm, fully implemented in software, was able to sense via a single ventricular electrode both the evoked T-wave and the spontaneous QRS. Using successive timing differences, the ventricular pacing rate could be adjusted automatically to increase cardiac output, based on changes in the QT interval. Since the first generation rate response pacemaker, by 1988 several generations of the dynamic rate response have been implemented in Quintech TX with over 4000 pacemakers<sup>67</sup> (Fig 7).

As with the Quintech DPG pacemaker, the Quintech TX pacemaker is programmed and routinely checked using standard Vitatron telemetry equipment, a Vitatron programming

head and an HP 85 desk computer.

#### **European Inventor Award 2007 - Nominee.**

In 1995, a patent<sup>68</sup> invented by 3 Vitatron staff - building on the 1982 Quintech TX Rate Response efforts - had a dramatic effect on the quality of life experienced by pacemaker users. The inventors created a pacemaker with dynamic, non-linear rate responsiveness - a product that completely automatically adjusts itself from patient to patient, as well as to patient history. In the years that followed, a number of products utilised this technology. It still features today in Vitatron pacemakers.<sup>69</sup>

#### **Dual-Chamber Pacemakers**

##### **1984 - From one to two leads**

The third microprocessor device introduced by Vitatron in 1984 is the **Quintech DDD** pacemaker. This is a dual chamber / dual leads pacemaker, specifically designed towards the management of atrial arrhythmias and to ease their follow-up. The pacemaker can continuously analyse cardiac activity, recognise various atrial rhythm patterns and optimise the response of the pacemaker. The device can automatically provide a Wenckebach type response for high atrial rates, rate adaptive AV delays and non-invasive analysis of retrograde conduction. The so-called 'flywheel'<sup>70</sup> mode guarantees stable haemodynamics by adaptation of the pacing rate in response to a spontaneous rate (Fig. 8).

#### **Ceryx Pacemakers**

##### **1983 - Programmable VVI workhorses**

Shortly after the introduction of the Quintech series, Vitatron released in 1983 a new range of single-chamber, multi-(re)programmable pacemakers under the name Ceryx.<sup>71,72</sup> The Ceryx 1 series is meant as a simple, rate programmable ventricle demand pacemaker with excellent longevity. Ceryx 3 provides additional flexibility to adjust stimulation parameters to individual patients as well as step-down for threshold measurements; Ceryx 6 provides even more programmable parameters and analysis opportunities. All three use the pacing threshold measurement, using the Vitatron step-down mode. As with the Quintech family, each Ceryx device has bi-directional telemetry technology to upload settings from a dedicated Vitatron medical programmer TP1.<sup>73</sup> At the same time, required information is downloaded from the pacemaker to the programmer to analyse the results and, where required, to adjust the pacemaker.

The Ceryx pacemaker series were real 'workhorses' for Vitatron. By 1990, 7 years after its introduction, the company reported to have over 41,000 implants<sup>74</sup> of the Ceryx pacemakers (Fig. 9).



Fig. 8 V32995 - *Quintech DDD*, first dual chamber / dual lead pacemaker with automatic arrhythmia detection, model 931, 1984 onwards.



Fig. 9 V33085 - *Ceryx 1*, single chamber VVI multi-programmable pacemaker, model 121, 1983.

#### **A Financial Balancing Act**

Ever since Vitatron started to produce its pacemakers in 1963, the company operated as a two-division company: Vitatron Medical and Vitatron Scientific. Whereas Medical developed and produced pacemakers and related equipment, Vitatron Scientific continued to operate a large range of laboratory-, clinical- and blood analysis apparatus. Over the years, the company grew steadily.

On the 6<sup>th</sup> of May 1976, Mr Eikmans, in his capacity as CEO of Vitatron NV, received the prestigious King Willem I prize.<sup>75</sup> This prize, issued every two years, is a recognition of entrepreneurship, endeavour and innovation. It recognised that Eikmans, through Vitatron, had inserted various significant impulses into the Dutch economy.

In 1977, the company had a turnover of some Nlg 51 mln<sup>76</sup> and a profit of Nlg 2.3 mln. The performance over 1978 was similar. Halfway that year, Vitatron announced that it was about

to start a new facility in Poland for production of lithium powered pacemakers.<sup>77</sup>

The company had always been looking for new ways to further finance its product developments as well as its global commercialisation. To generate new capital, Vitatron had been looking to consider an initial public offering (IPO) by issuing shares. After considerations, Vitatron opted to place these at the London Stock Exchange on 22 October 1979.<sup>78</sup> It was the first time that a Dutch company issued these at the LSE, without going to the Amsterdam stock market.

By the end of 1979, Vitatron booked a turnover of some Nlg 56 mln at a profit of almost Nlg 4 mln.<sup>79</sup> As a result, the company proposed to pay a dividend of 22.5 cents per share.

By late 1979, experts had forecasted that a growth of some 10% over 1980 in the pacemaker market could be anticipated. That prediction, however, did not materialise, in particular for the last quarter of the year. For the first half of 1980, the company still made a small profit of Nlg 16k at a turnover of Nlg 27.9 mln. By the end of 1980, Vitatron had become Europe's largest pacemaker, producing 13,000 pacemakers that year.<sup>80</sup>

When in March 1981 the full financial results over 1980 became available, Vitatron had to announce a significant loss of *minus* Nlg 3 mln. As a consequence, an extensive cost reduction exercise had to be implemented. The company had to part with 55 of 355 staff. In addition, almost 100 staff were subject to a working hours reduction.

As pacemakers now lasted much longer, demand for replacement pacemakers reduced. In addition, competition was growing while overall government budgets had been reduced. Hospitals had become very critical of their budgets and costs.<sup>81</sup>

In 1983, after a fundamental restructuring of the company, Vitatron was split into Vitatron Medical and Vitatron Scientific. In that year, a result of *minus* Nlg 2.2 Mln was recorded while turnover grew to Nlg 43 Mln.<sup>82</sup> A year later, Vitatron Scientific was sold and became Vital Scientific.

By April 1984, Vitatron issued a second series of shares - also at LSE - at a value of Nlg 8 Mln.<sup>83</sup> By the end of 1984, after 4 years, Vitatron had again obtained a positive result, just over Nlg 1 Mln. This result coincided with the departure of Vitatron's founder and director Mr. AH Eikmans.<sup>84</sup> He was succeeded by interim CEO Mr. Broos.

Halfway through the eighties, Vitatron had insufficient funds to continue significant production development, let alone to pursue a

global commercialisation of new products. The result of an initial public offering was also limited. For investors, the pacemaker industry was seen to be too risky, given the high liability risks. Even in the US, only specialised venture capitalists were willing to consider medical products like pacemakers. Next, Vitatron tried to partner with Philips Medical Systems, but Philips did not want to consider the company. 'Our implantation technology is very specific; Philips got rather concerned by this type of product liability', when Rob ten Hoedt, Vitatron's General Manager<sup>85</sup> in 2001, looked back at the difficult years.

The medical giant Medtronic had already been interested in Vitatron since 1982, when it introduced its Rate Response technology. Medtronic remained interested, when new Vitatron's Quintech TX generations were released. When Medtronic stated their interest in Vitatron's advanced technology as well as its good standing in the medical world, the company from Dieren felt ready to be acquired by Medtronic. Vitatron had two key reasons to consider Medtronic's offer: the pacemaker market was about 'flat' (in terms of production levels), while prices were under pressure. Secondly, as the American company was financially strong, it would be able to give Vitatron support in funding ongoing, expensive R&D.

In February 1985, Vitatron's Board accepted Medtronic's offer, recommending to its shareholders to transition Vitatron as an independent daughter company of Medtronic. By March 1986, over 85% of Vitatron's outstanding shares had been accepted and taken over by Medtronic for Nlg 32 mln.<sup>86</sup> The Dutch company Vitatron NV including its patents<sup>87</sup> had been sold and taken over by Medtronic Inc, USA. Vitatron Inc. expanded the Ceryx, Quintech and the new Diamond family of pacemakers out of Dieren and later nearby Arnhem. In 2005, Vitatron ceased all its pacemaker development in the Netherlands.

## Notes and References

1. Kees Ruitenbeek (KR) is with Rijksmuseum Boerhaave (RMB) in Leiden. Referenced pacemakers and leads from the Boerhaave collection are indicated as V34040 etc. In November 2008, RMB received a series of Vitatron pacemakers, ranging from its inception until 2007, when the company discontinued its production in the Netherlands. A summary version of this article in Dutch has been included on the Rijksmuseum Boerhaave website under 'Verhalen uit de collectie'.

2. J.W. Van den Berg, J.N. Homan van der Heide, J. Nieveen, E. Boonstra and D. Kramer, 'An implantable transistorized pacemaker for the (human) heart with two gears and control of the resistance of the tissues, the

electrodes and the pacemaker, *Proc. KNAW C* (1962), pp. 407-422.

3. 1952 - Paul Zoll, USA, invention of an external pacemaker that operated for more than 52 hours before spontaneous heart rhythm of the patient was resumed.

4. 1958 - Seymour Furman, USA, introduced a temporary, endocardial catheter electrode to maintain a patient for many weeks with an external pacemaker. *Surg. Forum*, **9**, (1958), pp. 245-249.

5. Arne Larsson was the recipient of the first, definitive electronic pacemaker, implanted by Senning and Elmquist, Sweden on October 8, 1958. Device was made by Elema-Schoenander, later Siemens - Elema. Pacemaker was powered using nickel-cadmium cells and inductively recharged. It would continue to 'fire' for a few hours. The second unit lasted for a week. Further (22!) replacements and numerous surgical interventions followed, until Mr Larsson died in 2001.

6. General pacemaker developments have been extensively covered by Patrik Hidefjall, *The pace of innovation* (Linköping University, 1997), and by Keith Jeffry, *Machines in our hearts* (John Hopkins University Press, 2001). Also by Tom Kenny, *Nuts and Bolts of Cardiac Pacing*, 2nd ed. (Wiley-Blackwell, 2008).

7. Comments by Wim Boute, Vitatron's past R&D Director, on an earlier version of this article are greatly acknowledged.

8. KR briefly interviewed prof Homan van der Heide by phone on 17/5/2018.

9. On 30 January 1962, Dr Gerard Brom, Thorax Surgery, Leiden University implanted an Elema-Schoenander pacemaker, a *first* in the Netherlands. Elema had manufactured 10 units for Leiden. Within the year, Groningen-made pacemakers replaced three Elema units.

10. See Van den Berg et al (note 2), p. 411: The 2-gears pacemaker was switchable via a small, yet powerful magnet, external to the body. In the first gear, it delivered 65 rpm for 'normal' use; the second gear, 85 rpm, was intended for moderate work or to increase cardiac output during infection illness. Impulse duration about 2 ms; dimension 9.2x4.4x2.2 cm<sup>3</sup>; size 150 grs. The pacemaker has two electrodes, the negative to be connected in the heart.

11. Van den Berg estimated that pacemaker in first gear would last about 5 years. Clinicians were dismayed to find that pacemakers lasted about 2 years on average. Cells were depleted nearly as much from self-discharged as from pacing. Of greater concern was that

cells emitted hydrogen gas as a by-product. Thus the pacemaker could not be sealed hermetically against intrusion of body fluids. 'If a really good power source were available ... a majority of pacemaker replacements could be avoided', Parsonnet wrote in 1970. K. Jeffry, *Cardiac pacing 1960-1985, 1978-1991, Circulation, 1998*.

12. The pacemaker would operate independent of the heart, hence 'asynchrone'.

13. First generation pacemaker patients received their pacemaker requiring a left anterior thoracotomy and exposure of the myocardium. Thus training in thoracic or cardiovascular surgery was absolutely necessary. K. Jeffry, *Cardiac pacing 1960-1985, 1978-1991, Circulation, 1998*.

14. Thalen's original thesis plan was to describe the Groningen research. It became clear that there was a serious gap (--) on the subject of cardiac stimulation... (hence he had)...to include a systematic survey.

15. H.J.T. Thalen, *The artificial cardiac pacemaker – its history, development and clinical application, PhD thesis, 1969*. Supervisor was prof. JW van den Berg. Thalen (1938) started as a student assistant and finished his medical studies in 1969. By 1979, he became cardiac consultant and head of the Pacemaker Clinic at the University Hospital, all in Groningen. Thalen suddenly died on 10 October 1982. *NedTGeneesk.* 126 NO 45, 1982.

16. Van den Berg initially contacted Mr Schuimer, a colleague from Groningen University, who knew Vitatron as a Dutch producer of clinical chemistry equipment.

17. Interview KR with Vitatron's founder and first CEO AH Eikmans on 9/11/2018. He started his company Vitatron in 1956, initially from his bedroom at Valeriusstraat 266, Amsterdam.

18. To take over production activities from Groningen University, Vitatron was looking for suitable office- and workshop facilities. It found a defunct leather workshop at the Spoorstraat, Dieren, the Netherlands. When activities grew further, in June 1977 the company started to construct a dedicated facility at an industrial area, Kanaalweg, Dieren. Eventually, the building was vacated in December 2002.

19. On technology push: when Thalen was still a student, Vitatron's Eikmans had sent him to Japan to study the latest on cardiology and pacemakers, NRC 4 10 1979.

20. J.N. Homan van der Heide, *The pacemaker of the 90's: Essentials in Brady pacing,*

(Springer, 1995), ed. Preface, pp. ix-xii.

21. In a panel discussion on longevity in 'Advances in Cardiac Pacemakers' in 1968, Thalen commented 'we (Th and van den Berg) developed it, but the Vitatron people are making it.'

22. MIP-100 was nick-named as the 'Groningen' pacemaker, in recognition of its Groningen developing team.

23. In 1967, Vitatron successfully introduced its 'intramural loop' electrode. A double electrode between pacemaker and the actual electrode -which forms the negative electrode of the system- would be covered by heart muscle tissue to become firmly connected to the myocardium.

24. Vitatron introduced the Pacemaker Monitor MPM100, a device to track the performance of the pacemaker, before and shortly after the implantation of the pacemaker in the patient. The Vitatron MCT100 cardio-test allows to check electrodes and to validate the (lowest) stimulation threshold of the heart.

25. Vitatron MIP-100 Pacemaker, Medical World News, June 3, p.129, 1966.

26. Investments to market and support this product on a global scale were very significant. Net results were rather limited. Eventually, Vitatron withdrew in 1979 from the USA market.

27. In fact all pacemaker manufacturers at that time followed this approach.

28. This pacemaker was initially developed to avoid interference between pacemaker rhythm and proper heart rhythm using a built-in magnetic switch. Vitatron MIP400R catalogue.

29. Thalen, *PhD thesis* (note 15), p. 256-257, Fig VIII-18; Hidefjall, *PhD thesis*(note 6), pp. 107-108; Also known as van den Berg & Thalen's (ventricle) R-wave blocked on demand, pp. 896-898, *Advances in Cardiac Pacemakers, New York Academy of Sciences, November 17-19, 1969*.

30. By 1969, Vitatron's product range consisted of asynchronous dual rate MIP150/ MIP500T pacemakers, a high power dual rate MIP250, a single rate MIP300 and a paediatric MIP150K. Furthermore, an R-blocked 'on demand' MIP400R was available. Electrodes included (intramural) MIP125 / paediatric MIP125S and (intracardiac) MIP140/45/47. Electrodes adapters and accessories MIP610/20/30. Vitatron Pacemaker Analyser MTA100, Vitatron Cardio test MCT200.

31. This opened opportunities to pin-point pacing at either ventricle or atrium (or even

later development with *two* leads). See also: ICHD / NGB code for pacemakers, 3 letter code *Am. J. Cardiol.*, **34** (October 1974); 5 letter code, updated in 2000.

32. Thalen: 'In 1962-1966 some problems with the epoxy that was used. After one and a half years, 50% of the pacemakers were defective. Since changing the epoxy in January 1967, only 8 out of 2000 pacemakers have returned. None of the 300 (MIP400R) demand units in clinical use have been returned as yet'. p. 900, *Advances in Cardiac Pacemakers, New York Academy of Sciences, November 17-19, 1969*.

33. In my interview of 9/11/2018, Vitatron's director Eikmans mentioned that a (Greek) medical journal had suggested the silicone layer around the epoxy might be carcinogenic. Thalen had investigated this and concluded that this was not the case.

34. Model range MIP 40RT through 501T, ran from 4/1972 to 11/1979 and produced some 268,000 pacemakers. Vitatron had its own R&D well in place when these series were developed.

35. Developments in pacemaker technology would take at least 2 to 4 years before fully accepted and routinely implemented. This process could be prolonged by extensive clinical (patient) tests.

36. Thereafter, 6 months pro rata.

37. Individual electronic elements require to meet USA MIL specs 883.

38. When a patient's heart rhythm would run at 70 rpm or higher, the pacemaker would operate in 'demand' mode.

39. VCA - Vitatron Completely Analysable technology: to check a series of key parameters such as diagnosing the battery status and test connections including the electrode.

40. Over the period August 1, 1975-July 1, 1977 19,300 pacemakers of the series MIP-42RT/43RT were delivered. Average failure rate was 0.007%.

41. As it was for nearly all other pacemaker production companies. Vitatron applied nearly always Mallory RM1 batteries.

42. The Lithium battery p. 1983, K. Jeffry, *Cardiac pacing 1960-1985, 1978-1991, Circulation, 1998*.

43. Wilson Greatbatch, like Senning and Elmqvist, had been involved in constructing and implanting cardiac pacemakers since 1960, 88, Jeffry, *Machines in our hearts*, 2001, John Hopkins University Press.

44. W. Greatbatch, *Pacemaker energy sources,*

- old and new*. In H.J.T. Thalen et al., *To pace or not to pace* (Martinus Nijhof, 1978), Mallory Ruben zinc-mercury batteries dominated the field from 1960 through 1975. By 1970, 50% of implanted pacemakers were removed in under two years, usually because of battery failure. Pacemakers could not be hermetically sealed. In 1970, lithium with iodine cathode was introduced. A USA 1978 survey on pacemaker sources indicated that only 5% of the impulse generators still used mercury-zinc batteries.
45. In fact three separate series: C-1/2/4000, P-1/3/4000 and S-3/6000; in this article treated as one.
46. Vitatron wanted to have at least two battery suppliers to ensure a fall back in case of production issues. It selected the companies SAFT, CRC and WGL.
47. Options to purchase the required integrated technology through the company ITT failed. Vitatron was unable to establish its own QC staff at the ITT facilities.
48. Vitatron Medical Techno-Logic: *Series on new technologies in Microelectronics*, 1978/9
49. Vitarel continued to produce for Vitatron until the company was sold to Medtronic in 1986 when Micro-Rel, a subsidiary of Medtronic, took over the chip production.
50. The P4122 impulse generator (0.5 ms) has a programmable rate between 50 and 125 rps. Idem P4142, 1 ms.
51. In 1968, Vitatron had already developed the concept of non-invasive threshold measurements. The threshold value is the electrical value above which the heart reacts on pulses of the pacemaker. Below this value, the heart will not respond to the pacemaker pulse. In case a pacemaker generates well above the threshold value, it will reduce the battery duration/longevity unnecessary.
52. Compare MIP42RT (1974, 70x47x20 mm<sup>3</sup>, 119 gf, 2.5 years) with P4122 (1979, 57x47x12 mm<sup>3</sup>, 56 gf, 15 years).
53. Based on an 8 bit RCA1802 CMOS processor.
54. Vitatron DPG: ventricular stimulation: VVI, VVT, or VOO. Also arterial stimulation: AAI, AAT or AOO.
55. Traditionally, a Holter device is a battery operated device, which continuously externally measures and records heart activities using histograms on a 24 or 48 hour basis.
56. Arrhythmia modes: automatic underdrive, dynamic overdrive and flywheel, e.g. Tachy-, brady- and premature heart beats to prevent or to finalise arrhythmia.
57. A Hewlett-Packard 85 multipurpose desk computer is routinely used in programming and analysis of the Quintech DPG.
58. Dedicated communication software between pacemaker and Vitatron programmable PH1 (V33073) (nicknamed 'dog's bone') is in place to protect the transmission. In case of communication errors, the pacemaker will operate according to predefined default values (also known as the magnet rate).
59. A Dutch newspaper (*Leeuwarder Courant* 18/3/1983) reported successful clinical trials with Vitatron's Quintech DPG involving some 200 people.
60. Note that van den Berg in 1962 already considered a two-gear pacemaker to accommodate a choice between a 'normal' and a 'moderate' work using a powerful magnet to select the pacing rate.
61. Metabolism: all chemical reactions involving in maintaining the living status of cells and organisms.
62. More correctly: the 'stimulus to evoked T-wave interval'.
63. A.F. Rickards, et al. *Effects of heart rate on QT interval (abstract)*. In: C. Meere, ed., *Proc of the VI world symposium on cardiac pacing* (Montreal, 1979) 2: 7. Also: A.F. Rickards, J. Norman, *Relation between QT interval and heart rate*, Br Heart J, 1981; 45: pp. 56-61.
64. David R. Ramsdale and R. Rao, *Cardiac Pacing and Device Therapy* (Springer, 2012), pp. 39-40.
65. In 1978 Vitatron had entered into a confidential agreement with Dr Rickards to progress this research. See also p. 229, P. Hidefjall, *The pace of innovation* (Linköping University Press, 1997).
66. The device was named TX, after Tony (AT) Rickards.
67. VVIR: various dynamic rate dependent slopes have been implemented: TX1 (1981); TX911 manual slope (1984); TX915 fu slope (1985); TX919 dd slope (1988).
68. EPO filing 29.9.89 - published 29.11.1995. See also US Patent 4,972,834. *Pacemaker with improved dynamic rate responsiveness*, M. Begemann, W. Boute, M. van Gemert, Vitatron Medical.
69. From the three nominees, the overall winner in 2007 was the Bosch airbag.
70. The 'flywheel' algorithm considers atrial interval variations with a lengthening of less than 12.5% of the previous interval and a shortening of less than 50 msec as physiological variations in the heart rate.
71. According to Vitatron's inhouse news magazine *Vitaal*, 1986/3: Since the introduction of Quintech, Ceryx and Onyx, hardly any CPS series were sold.
72. Onyx 101 and Onyx 401 VVI pacemakers were released in 1986 as 'budget' versions of the Ceryx with limited reprogrammable facilities.
73. In later years, HP85 computers were replaced by Vitatron hand-programmers TP1, TP2 (V34061).
74. Long-term survival probability: 99,79%.
75. Issued by the Commissaris der Koningin Mr Geertsema.
76. Approximately 20 M US\$. Nlg (or NLG) denotes the Dutch guilder, now an obsolete currency; mln contraction for million(s).
77. Vitatron Poland production 15/9/1977,14/8/78 NRC.
78. Vitatron issued 890.000 at Nlg 0,25 *Telegraaf* 17.10.1979.
79. Over 1979: Scientific and Medical contributed about equal to the financial results.
80. Vitatron also reported that some 600 repeated pacemaker-patients had slight corrosion on the electrodes. This was the first recall since 1973. *Vrije Volk* 18/12/80.
81. According to Vitatron's Finance Director Keimpema - *Telegraaf* 11/3/81.
82. This figure was adjusted to Nlg 37.2 Mln after the sale of Vitatron's Scientific division.
83. *Volkskrant* 22/2/84: 2<sup>nd</sup> issue LSE 320.000 exchange rate 2.70 . By 1/5/1985, dividend was Nlg 0,17/ share.
84. Eikmans mentioned in my interview that he had to learn to listen very carefully to (the) two groups in the company: the Board of Directors and the Industrial Council. 'When both indicate that it is time to go, you have to go'.
85. Rob ten Hoedt, General Manager Vitatron (1999 - 2006), spoke in an interview (21/12/2001, *Financieel Dagblad*) on the 'European testing bed for Technology' on Vitatron before the company became fully owned by Medtronic.
86. *Financieel Dagblad* - 18/4/86
87. By 1986, Vitatron had obtained 32 patents in 20 patent classes, see p. 376 in Patrik Hidefjall, *The pace of innovation* (Linköping University, 1997)

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