LifeTrack™ technology: detecting all breaks in the cold chain

Introduction:

Many foods, drugs, diagnostics, and other materials are perishable. Their stability is usually a function of their thermal history, and their deterioration is usually accelerated by exposure to higher temperatures for longer periods of time. This is a particular problem during cold-chain breaks. Since exposure to high temperatures for too long can render materials unusable, time-temperature indicators (TTI) or electronic temperature loggers are often used to warn when this type of problem has occurred.

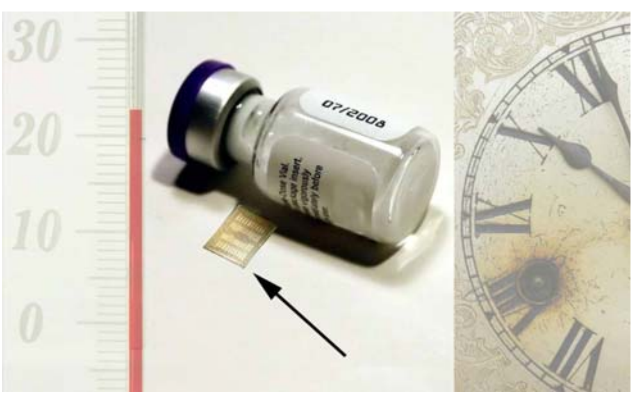
Temperature loggers are cumbersome to use because they must be downloaded and analyzed before the status of the material can be evaluated. By contrast, although TTI (which are small tags that ride along with a material, and monitor the acceptability of the material's thermal history) allow a material to be immediately evaluated, previous TTI were difficult to read consistently. This is because they were chemically based indicators that were difficult to tune precisely, and were read by visual colorimetric comparison

Ideally, what is needed is a device that would understand the stability characteristics of the material in question, continually monitor the material's thermal history, instantly let users know if the material is still good, and provide supplemental data as needed.

The ideal device is now here. CliniSense Corporation is proud to introduce LifeTrack™ technology[1]. This recently patented technology allows electronic tags, such as RFID tags, low-cost visual tags, and other devices to be easily customized to match the stability profile of any material of interest, warn when appropriate, and give data when needed.

LifeTrack technology incorporated into RFID and visual tags

RFID tag with LifeTrack technology



Technology demonstrator unit

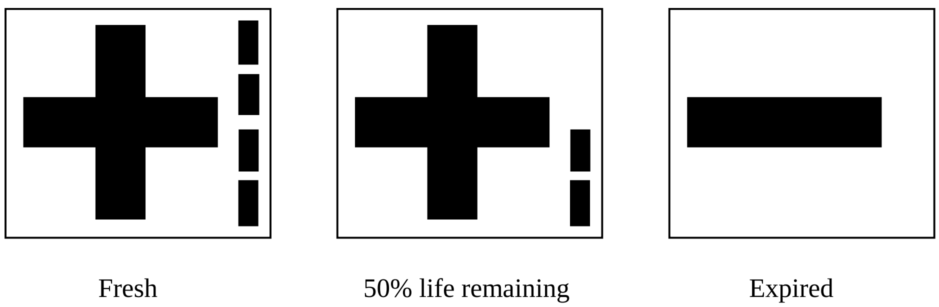
Stability monitoring tags using LifeTrack technology can have any type of output, including visual, sonic, radio, or electronic (such as Internet messaging). The technology

[1] US patent 6,950,028; other US and foreign patents pending

is ideal for battery assisted passive RFID tags. CliniSense licenses this technology on a non-exclusive basis, and also provides an easy way to get started: the demonstration unit.

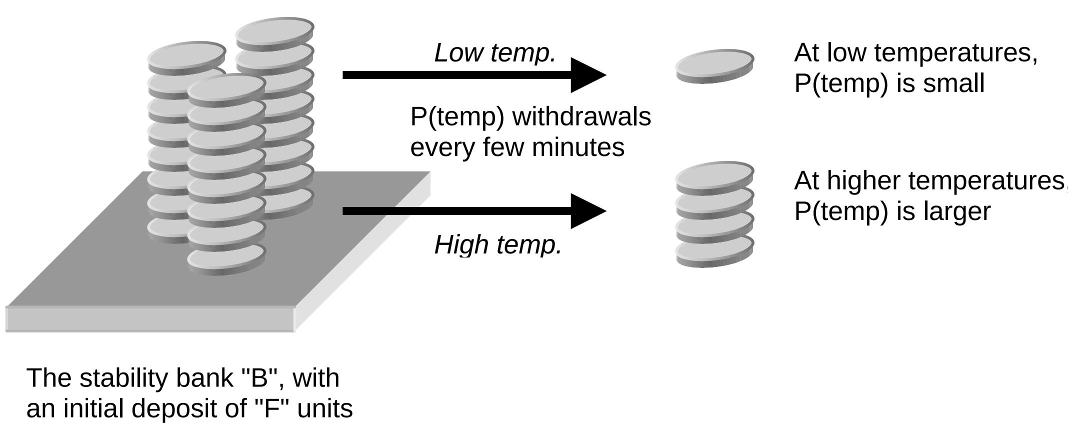
The LifeTrack technology demonstration unit is a low-cost and immediately available way to evaluate this technology. Demonstrator units can be rapidly customized to your particular application. For simplicity, these units have a visual "+/-" display, a bar graph showing the percentage of the original shelf life that is remaining, and an infrared port allowing output of "flight recorder" type temperature logging and statistical data.

LifeTrack technology demonstrator display, showing remaining material lifetime

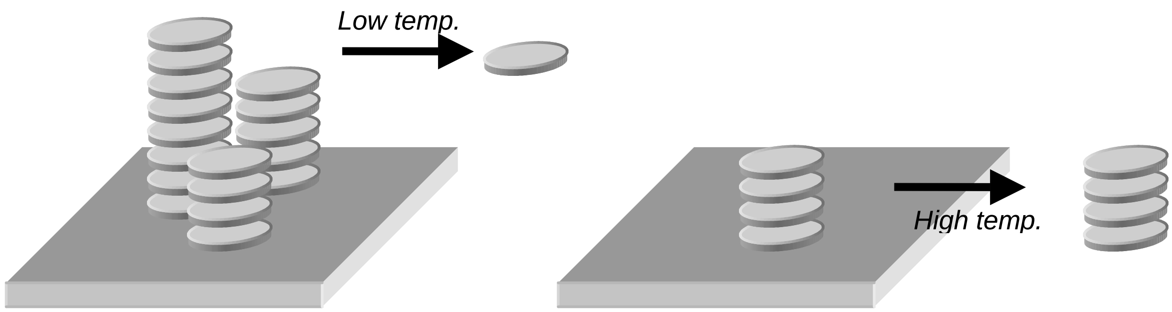


How it works -- the "stability bank" concept:

LifeTrack technology uses a new concept, called the "stability bank" model. Here, a material's stability is tracked by the status of a stability bank account (B). This account is opened (for fresh material) with an initial deposit of "F" stability points. Every few minutes, "P" stability points are withdrawn from the account. The number of stability points "P" withdrawn each time is a variable that is a function of temperature, P(temp). At low temperatures, a small number of stability points "P" are withdrawn from the bank every few minutes. At higher temperatures, a larger number of stability points "P" are withdrawn from the bank every few minutes.



As the material ages, the amount of stability points remaining in the stability bank (B) decreases. When the stability bank account "B" hits zero, the material has expired.



Stability bank "B" after several minutes at low temperature

Stability bank "B" after several minutes at high temperature

Mathematically, if the stability bank account "B" of the fresh material is "F", and P(temp) stability points are withdrawn every 60 minutes (1 hour), then the status of the stability bank account "B" at "Time" (or "T") hours later is:

$$(1) \quad B = F - \sum_{0}^{Time} P(temp)$$

If B is > 0, then the material is still good. If B <= 0, then the material has expired. Using the stability bank model, and appropriate selection of "F" and P(temp) values, the stability characteristics of nearly any material can be accurately modeled.

The LifeTrack Technology Demonstration Unit:

The LifeTrack technology demonstration unit is an electronic device containing a microprocessor, temperature sensor, battery, and display. The microprocessor is programmed to make periodic temperature measurements, convert the measurements into the appropriate P(temp) values, and then perform stability calculation (1). If the stability bank "B" value remains positive, the eTTI will display a "material good" prompt, such as a "+". If the stability bank "B" value becomes zero or negative, the LifeTrack will display a "material expired" prompt, such as a "-".

The demonstrator unit is available in both programmable and non-programmable models. In the non-programmable model, a predetermined "F" value and table of P(temp) values are programmed into the microprocessor's read only memory (ROM). This is suited to high volume applications where cost is more important than flexibility.

The programmable version of the LifeTrack technology demonstrator contains a data input jack, and Flash memory. Thus "F" and P(temp) values may be rapidly downloaded into the unit, and the unit customized to nearly any application. Programmable LifeTrack technology demonstration units are well suited for feasibility studies, and low and medium volume applications where implementation speed and flexibility are desired.

Programming and customizing a demonstration unit:

Preliminary experiments and calculations: In order to properly configure a LifeTrack, the manufacturer must first characterize the stability of the material that the LifeTrack will be monitoring. To do this, the manufacturer should first set quantitative "maximum acceptable deterioration" criteria, and then determine the material's stability lifetime at a variety of temperatures. The stability lifetime at the various experimental temperature levels is then determined, and used as input into the LifeTrack programming calculations.

Using the experimental data, a curve or equation is then generated that fits the observed data. This curve is used to calculate the stability lifetime at intermediate temperatures.

As an example, consider a commonly used injectable drug, insulin. Insulin is commonly carried by traveling diabetics, but will deteriorate if exposed to excessive levels of temperature for too long. The work of Brange et. al.[2] determined that a particular type of insulin, called "ultralente insulin", has the following stability characteristics:

Table 1: Experimental Insulin stability data

Insulin stability at various temperatures (^oC)				
Insulin type	4 ^oC	15 ^oC	25 ^oC	40 ^oC
Ultralente	19 years	2 years	4 months	1 week

Additionally, although it is not shown on table 1, it is also known that insulin is rapidly damaged by freezing, and rapidly damaged by extreme heat. These "boundary conditions" will be discussed shortly.

Returning to table 1, note that at the point of maximum stability (4 ^oC), the insulin has a fresh lifetime "F" of 19 years, or 165984 hours. Thus, in this example, using hours for the time units:

F = number of time units at optimum stability temperature = 165984 hours.

So the stability bank "B" for fresh material will have an initial deposit of "F" (165984) units. Moreover, if the insulin is kept at a constant 4 ^oC temperature, $P(temp_{4C})$ should deduct 1 point per hour from the stability bank "B", and the stability equation (1) is:

[2] J. Brange in 'Galenics of Insulin' by J Brange M.Sc et al: [Novo Research Institute, Denmark] Springer-Verlag, 1987

(2) $B = F - \sum_{0}^{Time} P(temp_{4c})$ thus: $B = 165984 - \sum_{0}^{Time} 1$ or equivalently:

$B = 165984 - Time$

To determine the P(temp) values for temperatures above 4 ^{o}C, the experimental stability lifetime data is modeled by a best-fit equation. The nature of this equation will vary according to the specific material being modeled. In this example, the data from table 1 was converted into an "hours of lifetime" format, and analyzed using Microsoft Excel. Excel showed that the 4 ^{o}C to 40 ^{o}C insulin data fit the following exponential equation quite well:

(3) $Stability\_lifetime(hours) = 0.77\, e^{0.1752T}$ where "T" is the time in hours

To determine the P(temp) values for various temperatures, it is important to note that at a constant temperature, $temp_c$, equation (1) becomes:

(4) $B = F - P(temp_c)T$

Now by definition, the stability lifetime is the time "T" when the stability bank "B" first hits zero, so at the stability lifetime limit where B=0, equation (4) becomes:

(5) $0 = F - P(temp_c)T$ so solving for $P(temp_c)$, then

(6) $P(temp_c) = \frac{F}{T}$

Thus for any given temperature, $P(temp_c)$ is equivalent to the lifetime of the material "F" at the optimal stability temperature, divided by the calculated lifetime of the material at the particular given temperature ($temp_c$).

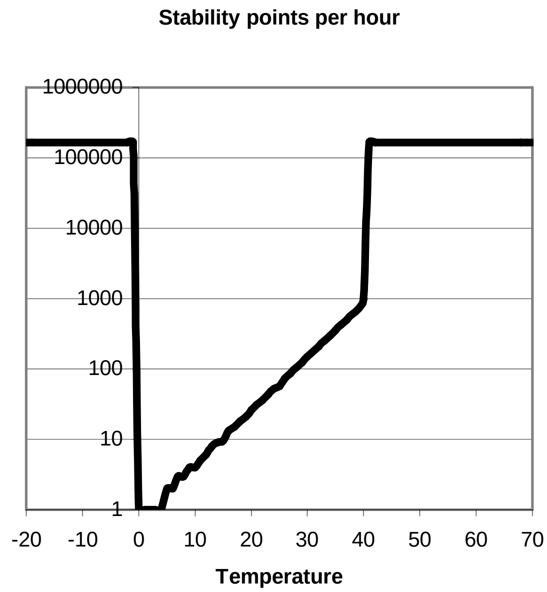
In this insulin stability example; the experimental data from table 1, the maximum stability lifetime "F" of 165984, and the best fit stability lifetime equation (3), can be combined with equation (6) to produce a table of P(temp) values that covers the temperature range between the 4 ^{o}C and 40 ^{o}C experimental data points.

Although the insulin stability data between the 4 ^{o}C and 40 ^{o}C data points fit the exponential equation (3) well, in practice, the real insulin stability function is somewhat "U" shaped. This is because insulin is severely damaged by freezing. Insulin is also rapidly damaged at very high temperatures.

LifeTrack technology is able to accurately model these boundary conditions as well. This is done by incorporating this additional temperature information into the unit's stability point lookup table. Here, temperatures below 0 ^{o}C, and temperatures above 40 ^{o}C, are given a very high number of stability points. As a result, if the unit encounters these conditions in the field, the insulin will properly be designated as "expired". The complete set of P(temp) calculations, including these boundary conditions, is shown in Table 2.

Table 2: P(temp) calculations for Insulin stability between -20 to 70 ^{o}C

Temp ^{o}C	Lifetime Hours	P(temp)	Notes
-20	1	165983	Low boundary
			Low boundary
-1	1	165982	Low boundary
0	165984	165981	Low boundary
1	165984	1	
2	165984	1	
3	165984	1	
4	165984	1	Data point
5	82992	2	
6	82992	2	
13	20748	8	
14	18443	9	
15	17472	9.5	Data point
16	12768	13	
17	11066	15	
21	5354	31	
22	4611	36	
23	3860	43	
24	3192	52	
25	2912	57	Data point
26	2274	73	
38	277	600	
39	232	714	
40	168	988	Data point
41	1	165981	High boundary
			High boundary
70	1	165983	High boundary



Graph of insulin stability points vs. temperature (log scale) showing "U" shaped boundary regions surrounding the central exponential fit region

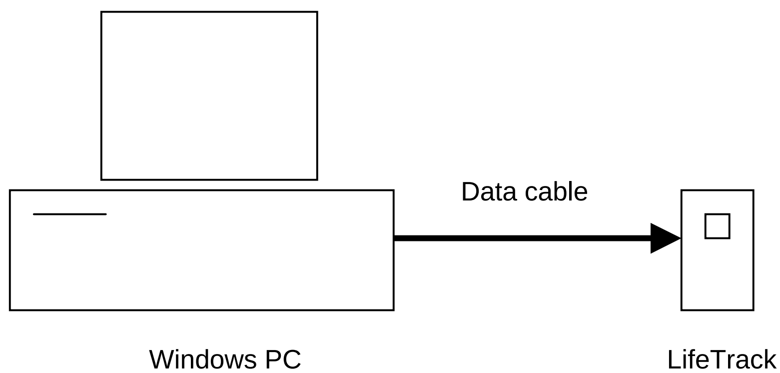
Note that for typical applications, such as field use diagnostic tests, Temperature data and P(temp) calculations will typically be performed every few minutes.

The same LifeTrack unit can be programmed to monitor materials with stabilities ranging between the stability of ice cream, and the stability of rocks.

Programming the LifeTrack units: After the "F" and P(temp) data have been calculated, the process of producing a customized LifeTrack demonstrator unit is simple. The "F" value and table of P(temp) values are downloaded electronically into the LifeTrack through the LifeTrack unit's data input jack. The programmed LifeTrack is then ready to use.

To do this, the table of P(temp) values is loaded into a LifeTrack data download program, which runs on a standard personal computer (PC). The LifeTrack is then connected to the PC's serial port via an adapter cable, and the data transferred. After the data is downloaded, the program and LifeTrack unit automatically check the success of the download by comparing the data to a checksum. A schematic of this download process is shown in the figure below:

Use of a PC and data cable to customize a LifeTrack unit



Before use, the LifeTrack units are subjected to additional QC testing and verification. To facilitate this process, the LifeTrack has the ability to operate in various "QC test" modes that test the unit at accelerated speeds, and report temperature sensor calibration by telemetry. These QC test modes enable large numbers of LifeTrack units to be calibrated, programmed, and tested using a high-volume, automated, manufacturing process.

After programming and appropriate QC verification, a QC security sticker (containing appropriate labeling) may be placed over the unit's test button, data port, and reset button to keep unauthorized users from tampering with the unit. The units have reset detecting security codes, and alternatively can be configured for one-time use (if desired).

To facilitate use in the manufacturing environment, the LifeTrack can be programmed with a variable "start of testing delay" value between 0 and 1440 minutes (1 day). This allows the manufacturer time to initialize, handle, and package the LifeTrack unit before monitoring begins.

Data logging and downloading: Why is that material expired? When and how did the thermal stress occur?

To answer these questions, the LifeTrack technology demonstrator has a 100-point data logger that records temperatures in intervals of n*30 minutes (n = 1 to 192). This allows the logger to record temperatures at intervals ranging from 30 minutes to 4 days, and for total times ranging between 50 hours to 400 days. The logger automatically records the time of material expiration, and saves the pre-expiration logger data for later playback. To enable expiration events to be precisely pinpointed, the logger also reports the time, average temperature, and deviation in temperature since expiration.

LifeTrack data logger download

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---------------------------------------------------------------------------
Mon Apr 26 09:46:19 2004

Cefepime, ID Code:  4P40001

Security code: 34953,  Checksum: 7342 vs 7342 OK

Status: OK (67.1 % life remaining)

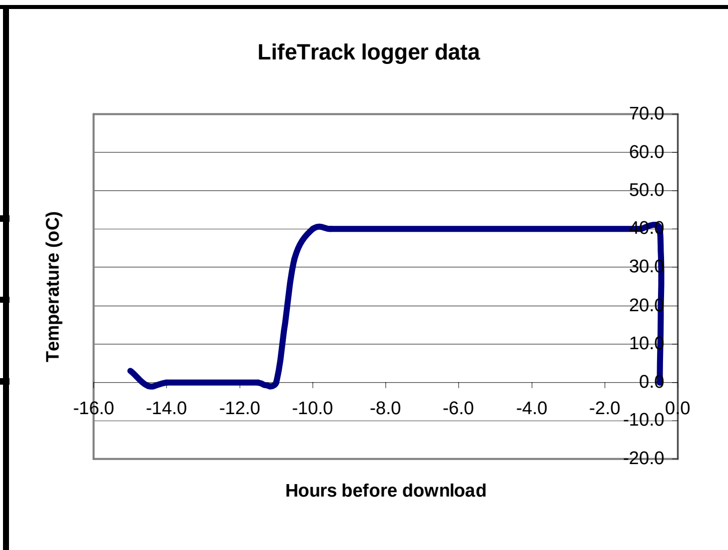
Hours elapsed since LifeTrack start: 15
Hours run: 15, Average temperature: 28.7 +/- 4.7 C


Temperature logger (degrees C):
Logger frequency: 0.5 hours, total logger time: 15.0 hours

Temperatures recorded
[-     15 hr.]    3,   -1,    0,    0,    0,    0,    0,    0,    0,   32,
[-     10 hr.]   40,   40,   40,   40,   40,   40,   40,   40,   40,   40,
[-      5 hr.]   40,   40,   40,   40,   40,   40,   40,   40,   40,   40,
[-      0 hr.]
Logger still running when downloaded.

Stress test 0 and 40 C
---------------------------------------------------------------------------
```

Download Date	Mon Apr 26 09:46:19 2004
Name	Cefepime
ID Code	4P40001
Security Code	34953
Status	OK
% Life remaining	67.1
Total hours running	15
Hours ran pre-expiration	15
Average temp	28.7
3x Deviation	14.1
Hours ran post-expiration	0
Average temp	NA
3x Deviation	0
Logger frequency	0.5
Hours of data logged	15.0
Logger start time	-15.0
Loger Status	Running
Hours since expired	0.0
Time expired	
Notes	Stress test 0 and 40 C



LifeTrack Technology Demonstration Unit Characteristics[3]:

Size: *2 1/4" x 1 1/2" x 0.5"*
Temperature range:[3] -20 - 70 °C
Temperature accuracy: +/- 0.5 - 1 °C, NIST factory calibration available
Time resolution: 1 - 60 minutes between each temperature time point
Time delay until monitoring starts: 0 - 1440 minutes
Interface: LCD, reset button, test button, data interface
Temperature logger: Last 100 temperatures before expiration (30 min - 4 day spacing)
Temperature statistics: Average pre-expiration & SD, average post-expiration & SD
Data Interface: 9600 Baud RS232 through onboard IR port
Battery: CR2032 (3V) coin cell
Battery lifetime: 24 to 36+ months
EMC optimized design
Humidity: 0 - 95%. The unit may be sealed in watertight covering for high humidity

Standard options (programmable unit):

Quick-turn factory programming
Data download cables and software
LifeTrack programming software & hardware
Assistance with programming calculations

Other configurations (for high volume customers):

Alternate display
Sonic or RF alarm
Extended battery lifetime
Extended temperature range
Alternate case or colors
Embedded

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[3] Typical commercial unit.

6/8/2006